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Health Technology Assessment

Tympanostomy Tubes in Children

Draft Evidence Report

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Tympanostomy Tubes in Children

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Abbreviations

Ad: adenoidectomy
Ad-Tons: adenotonsillectomy
AOM: acute otitis media
CI: confidence interval
CoE: class of evidence
dB: decibels
FDA: US Food and Drug Administration
f/u: follow-up
HTA: health technology assessment
HTE: heterogeneity of treatment effect
Hz: hertz
kHz: kilohertz
MD: mean difference
mos.: months
N: number of patients
NHS: National Health Services
NIH: National Institutes of Health
NA: not applicable
NC: not calculable
NR: not reported
NS: not statistically significant ($p \geq 0.05$)
OM: otitis media
OME: otitis media with effusion
RD: risk difference
RR: relative risk
SD: standard deviation
SoE: strength of evidence
SR: systematic review
Tons: tonsillectomy
TT: tympanostomy tubes
vs.: versus
WW: watchful waiting
yrs.: years

Executive Summary

Introduction

Middle ear inflammation, also known as otitis media (OM), is one of the most common childhood ailments, with a diagnostic frequency second only to upper respiratory infection.[64] It is estimated that by age one, 62% of children will have had at least one episode of OM.[14] OM often spontaneously resolves, but approximately 46% of children will have more than three episodes of OM with effusion (OME) by age 3.[14] As such, the short-term and long-term effects are significant due to the high prevalence of OM in the population.[7,15,20,25,27,36,39,41,48,54,61,70,72,74,76,80,81]

There is concern that OM—particularly long-term, persistent OM— reduces quality of life, incurs great economic costs, and impedes child development. OM can lead to fever and ear ache (otalgia), which can severely affect the quality of life (QoL) for both children and parents, resulting not only in physical and emotional discomfort for all involved, but also in missed days of school, missed days of work, and increased physician's office visits. The economic burden of this is enormous: in 1992, it was estimated that OM-related Medicaid costs were $555 million for children under the age of 14.[7]

Additionally, OM is linked with hearing loss[18]—while normal conductive hearing levels are under 20 dB,[64] otitis media with effusion is related to a conductive hearing level of 25-30 dB.[10] Due to this hearing loss, there is particular concern that children with chronic or recurrent OM may experience developmental delays. Some studies indicate that longer time spent with OM results poorer reading and verbal abilities and overall lower IQ.[52]

Otitis media with effusion (OME) is characterized by fluid in the middle ear without any symptoms of acute ear infection (e.g., fever, pain). It is estimated that 90% of children will have at least one episode of OME by age 10.[78] While many episodes of OME resolve spontaneously with no medical intervention, approximately 30 to 40% of OME cases will develop into chronic OME, which is characterized as OME that persists for at least three months.[72,74,80] OME is associated with an average 28 dB conductive hearing level—approximately 8 dB worse than children with normal hearing.[64] As a result of reduced hearing, there is concern that OME, especially chronic OME, may impact child development with regards to language, behavior, and academic achievement. Additionally, chronic OME has physiologic and anatomic adverse effects, including increased risk for cholesteatoma, characterized as accumulated keratinizing epithelium; retraction pockets and atelectasis, which are weakened portions of the ear drum that have collapsed; acute otitis media (AOM); cysts in the middle ear; and tympanic scarring.[53,64]

Acute otitis media (AOM), more commonly known as an ear infection, is bacterial or viral in nature and frequently presents as sudden onset of inflammation of the middle ear. Symptoms include ear pain, irritability, loss of balance, fever, and loss of hearing.[1] It has been shown that 15% to 20% of preschoolers will develop recurrent AOM,[63] which is defined as 3 or more separate episodes of AOM the past 6 months, or at least 4 separate episodes within the past 12 months with at least 1 in the past 6 months.[64] Similar to OME, children with AOM also have reduced hearing that may cause developmental delays, in addition to presenting with many of the same quality of life issues. As with OME, children with craniofacial disorders, Down syndrome, or cleft palate are also at increased risk for AOM, as Eustachian tube dysfunction is prevalent in these conditions.

Tympanostomy tube insertion is the primary surgical treatment for otitis media, and is performed in approximately 667,000 children each year.[16] Approximately 1 mm in diameter, functioning tubes equalize middle ear pressure with atmospheric pressure and allow fluid drainage, alleviating symptoms of otitis media. Tubes are indicated for drainage of chronic otitis media with effusion, or persistent acute otitis media that has failed medical therapy.[64] *Anticipated outcomes*

Tubes have been shown to be effective at managing chronic OME, with systematic reviews indicating that insertions reduce middle ear effusion by 32% in the first year and improve average hearing levels from 5-12 dB.[64] Tube efficacy at managing recurrent AOM is less supported, with many systematic reviews indicating little evidence or small short-term benefits.[64] Overall, tube insertions have been shown to improve quality of life for children and parents.[64] It should be noted that these are all systematic reviews that have been conducted in otherwise healthy children. Tubes have been shown to improving hearing, but these improvements dissipate in the long-term; a systematic review[9] for children receiving grommets with chronic OME showed that hearing benefit is greatest at 3 months, but is reduced at 6 to 9 months.

Tube placement is performed under general anesthesia, and tubes typically fall out within 12 to 14 months. Tympanostomy tubes may decrease the occurrence of otitis media, and may improve hearing and quality of life. Risks of tympanostomy tube insertion may include otorrhea, blockage of the tube lumen, granulation tissue formation, premature tube extrusion, and tube displacement. In addition, there are risks associated with use of general anesthesia. In the longer term, tympanostomy tubes may lead to changes in the eardrum as well as possible long-term hearing loss. Other treatment options include antibiotics or other medications such as steroids or mucolytics, myringotomy (eardrum incision), adenoidectomy, or autoinflation of the Eustachian tube. In addition, because otitis media often resolves spontaneously, especially within the first six months, and may not cause long-term hearing or developmental problems, watchful waiting or delayed tube placement may be considered.

Policy Context

There are significant questions related to the use of tympanostomy tubes for the treatment of otitis media with effusion in children under the age of 16 regarding efficacy, safety, differential efficacy and safety in subgroups, and cost.

Objectives

To systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of tympanostomy tubes in children for treating otitis media with or without effusion. The differential effectiveness and safety of tympanostomy tubes for subpopulations will be evaluated, as will the cost effectiveness.

Key Questions

In children aged 16 years and younger with either (a) chronic otitis media with effusion (OME) or (b) recurrent or persistent acute otitis media (AOM) (evaluated separately):

1. What is the evidence of the short- and long-term efficacy and effectiveness of tympanostomy tube insertion compared with alternative treatment options or watchful waiting? Under what circumstances are tympanostomy tubes indicated?
2. What is the evidence regarding short- and long-term harms and complications of placement of tympanostomy tubes compared with alternative treatment options or watchful waiting?
3. Is there evidence of differential efficacy, effectiveness, or safety of tympanostomy tubes compared with alternative treatment options or watchful waiting? Include consideration of age, sex, race, ethnicity, socioeconomic status, risk for developmental delay, repeated exposure to large groups of children, duration of otitis media, and recurrent acute versus chronic otitis media.

4. What is the evidence of cost-effectiveness of tympanostomy tubes compared with alternative treatment options?

Inclusion and exclusion criteria are summarized as follows:

- Population: Studies of children age 16 and younger who received tympanostomy tube (TT) insertion for either chronic otitis media with effusion (OME) or recurrent acute otitis media (AOM).
- Intervention: Included studies evaluated tympanostomy tubes.
- Comparators: Included studies compared TTs to watchful waiting (with or without delayed TT insertion), myringotomy, adenoidectomy, antibiotic therapy, mucolytics, steroids, autoinflation of the Eustachian tube, or complementary and alternative medicine treatments.
- Outcomes: Eligible studies reported on at least one of the following outcomes: hearing, otorrhea, recurrent AOM, recurrent OME, balance and coordination, cholesteatoma, attention and behavioral outcomes, academic achievement, auditory processing, speech and language development, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, patient quality of life, parent quality of life, pain, surgery, medication usage, number of office visits, or harms (including harms of TT, comparator treatment, or general anesthesia).
- Study design: Eligible studies compared TT with an included comparator treatment utilizing a randomized or cohort study design; nonrandomized comparative retrospective studies were considered if they included at least 100 patients and had complete follow-up of at least 80% of patients. Case series specifically designed to evaluate harms/adverse events that enrolled at least 500 patients and that had follow-up of at least 70% of patients were considered for Key Question 2. Only RCTs stratified on patient characteristics of interest and formally evaluated statistical interaction (effect modification) inclusion were considered for Key Question 3; subgroups of interest included otitis media duration, recurrent acute versus chronic otitis media, children at risk for developmental disabilities (i.e., permanent hearing loss (independent of otitis media) (including sensorineural hearing loss); speech and/or language delay or disorder; autism spectrum disorders; Down Syndrome; craniofacial disorders (e.g., cleft palate) that are associated with cognitive, speech, and/or language delays; blindness or uncorrectable visual impairment; developmental delay), age, sex, repeated exposure to large groups of children (e.g., daycare), race, or socioeconomic status. For Key question 4, formal economic analyses were eligible for inclusion; the emphasis was placed on studies based on patient outcomes (rather than those that used a hypothetical patient cohort).

Methods

The scope of this report and final key questions were refined based on input from clinical experts from a variety of disciplines and public comments received on draft key questions. Clinical expert input was sought to confirm critical outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature across a number of databases including PubMed to identify relevant peer reviewed literature as well as other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature.

Pertinent studies were critically appraised independently by two reviewers based on Spectrum's Class of Evidence (CoE) system which evaluates the methodological quality and potential for bias based on study

design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results: Summary of the highest quality evidence on critical outcomes

The following summaries of evidence are based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the critical outcomes for each key question are provided in the tables below and are sorted outcome. Full tables sorted by comparator are available in section 5. Details of these and other outcomes are available in the report.

Evidence base:

OME

- TT vs. WW: Seven RCTs reported across 20 publications[28-30,40,41,47,49-51,55-59,62,65-67,79,82]
- TT (unilateral) vs. no treatment (contralateral): Five RCTs reported across eight publications[5,19,38,42-46]
- TT vs. Myringotomy: Seven RCTs reported across eight publications[5,17,22,23,31,33,40,41]
- TT + Ad vs. Myringotomy + Ad: Eight RCTs reported across nine publications[5,12,22,23,60,68,69,73,77], two prospective cohort studies published across five papers[6,32,37,75,76 #825], and one retrospective cohort study was also included (Caye-Thomasen 2008[13])
- TT + Ad vs. Ad: Four RCTs reported across seven publications[5,8,19,43-46], and one prospective cohort study[2,3]
- TT vs. Myringotomy + Ad: Two RCTs reported across three publications[12,22,23].
- TT vs. Ad: Two RCTs reported across five publications[19,43-46]
- TT vs. Antibiotics: One RCT reported across two publications[4,71]
- TT vs. all other included comparators: No evidence

AOM

- TT vs. Antibiotics: Four RCTs[11,21,24,26]
- TT vs. Placebo or No treatment: Three RCTs reported across 4 publications[11,26,34,35]
- TT vs. all other included comparators: No evidence

AOM or OME

- TT (unilateral) vs. Myringotomy or No treatment (contralateral): One RCT[36]
- TT vs. all other included comparators: No evidence

Hearing levels*

***Summary*:** Hearing levels were reported for all comparators identified. Hearing levels were significantly better (i.e., 3-7 dB lower) in ears with tubes versus those without tubes between 3 and 9 months (varies with comparator) follow-up. This difference was not observed at later follow-up time points (ranging from 6-120 months).

Outcome	Follow-Up	Studies N	Comparative Impact: Hearing Levels	Quality	Age At Enrollment
TT Versus WW For OME	6-9 mos.	3 RCTs (COMET, TARGET, Rovers) N=522	At 6-9 months f/u, hearing levels were a mean of 4.39 dB lower (better) in the TT group (pooled MD: -4.39 dB, 95% CI -6.29 to -2.50 dB, p<0.00001). (All patients had bilateral OME and hearing loss at baseline.)	⊕⊕⊕◯ MODERATE	Age: 1.6-5.2 yrs. (range of means)
	12-18 mos.	3 RCTs (COMET, TARGET, Rovers) N=467	By 12-18 months f/u, hearing levels were similar between groups. (All patients had bilateral OME and hearing loss at baseline.)	⊕⊕⊕◯ MODERATE	Age: 1.6-5.2 yrs. (range of means)
	Age 6	1 RCT (Paradise) N=281	At age 6, mean hearing levels were similar between TT and WW groups. (At baseline, 71.5% of patients had hearing levels that were 20dB or higher; mean baseline hearing levels were not reported.)	⊕⊕⊕⊕ HIGH	Mean age: 1.25 yrs. (range 0.2-3 yrs.)
TT (Unilateral) Versus No Treatment (Contralateral) For OME	6 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Lildholdt) N=209 (418 ears)	At 6 months f/u, results from three studies (N=144) suggest a modest benefit (2-5 dB) with TT, while a fourth study (N=65) suggests a larger benefit (11 dB) with TT. Pooled data from 3 of these trials (N=137) suggest 6-month hearing levels were a mean of 6.5 dB lower (better) in the TT group (pooled MD -6.6, -14.8 to -7.8 dB, p=0.01) (3 RCTs, N=137). (All patients had bilateral OME and the majority had hearing loss at baseline.)	⊕⊕◯◯ LOW	Age: 3.9-6.0 yrs. (range of means in 3 RCTs); NR in 1 RCT (range 2-9 yrs.)
	12 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Lildholdt) N=218-220 (438 ears)	By 12 months f/u, pooled data from 3 RCTs indicated that hearing levels were similar between groups. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Age: 3.9-6.0 yrs. (range of means in 3 RCTs); NR in 1 RCT (range 2-9 yrs.)
	24 mos.	3 RCTs (Black, Maw & Bawden, Lildholdt) N=171-173 (344 ears)	At 24 months f/u, overall hearing levels were similar between groups. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Age: 3.9-6.0 yrs. (range of means in 2 RCTs); NR in 1 RCT (range 2-9 yrs.)

Outcome	Follow-Up	Studies N	Comparative Impact: Hearing Levels	Quality	Age At Enrollment
	36 mos.	2 RCTs (Maw & Bawden, Lildholdt) N=105-113 (218 ears)	At 36 months f/u, one trial found significantly better hearing in the TT ear than the no treatment ear (MD -3.7 dB, -7.3 to -0.1); this trial had reinserted tubes in 66% of TT ears by 36 months. The other trial (N=48) found no difference between groups (MD of 0 dB). No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 3.9 yrs. (in 1 RCT); NR in 1 RCT (range 2-9 yrs.)
	48 mos.	2 RCTs (Maw & Bawden, Lildholdt) N=81-89 (170 ears)	At 48 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: 3.9 yrs. (in 1 RCT); NR in 1 RCT (range 2-9 yrs.)
	60, 84, 120 mos.	1 RCT (Maw & Bawden) N=15-56 (35-103 ears)	At 60, 84, and 120 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: NR (range 2-9 yrs.)
TT Versus Myringotomy For OME	6 mos.	2 RCTs (Black, Kent) N=67	At 6 months f/u, hearing was better in the TT ear compared with the myringotomy ear: one RCT reported a mean improvement in hearing of 7.4 dB (95% CI, 1.4 to 13.4, p<0.05), and the other RCT reported that significantly fewer TT ears had “hearing impairment” (not defined) than those treated with thermal myringotomy alone (0% versus 17%, RD -17%, 95% CI -30% to -3%, p=0.0206).	⊕⊕◯◯ LOW	Age: 5.3-6.1 yrs. (range of means)
	12 mos.	2 RCTs (Black, D’Eredita) N=67	At 12 months f/u, hearing levels were similar between groups.	⊕⊕◯◯ LOW	Age: 3.7-6.1 yrs. (range of means)
	24 mos.	1 RCT (Black) N=277	At 24 months, hearing levels were similar in TT versus myringotomy ears.	⊕⊕◯◯ LOW	Mean age: 6.1 yrs.
	0-24 mos.	1 RCT (Gates) N=277	From baseline through 24 months, TT patients had hearing loss (hearing levels ≥20 dB) at 7% to 8.5% fewer audiometry evaluations than myringotomy patients as measured in both the better ear (10.1 ± 14.1% vs. 18.6 ± 19.5% of visits, RD -8.5%, 95% CI -12.5% to -4.5%, p<0.001) and in the worse ear (30.4 ± 22.7% vs. 37.5 ±	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)

Outcome	Follow-Up	Studies N	Comparative Impact: Hearing Levels	Quality	Age At Enrollment
			25.3% of visits, RD -7.1%, 95% CI -12.8% to -1.4%, p=0.0145).		
TT+Ad Versus Myringotomy+Ad For OME	3 mos.	1 RCT (To) N=108 (216 ears)	Hearing levels at 3 months were significantly better in the TT ear than the myringotomy ear (17.1 vs. 21.4 dB, mean difference -4.3 dB (95% CI not reported or calculable), p<0.05) in one trial of adenoidectomy patients.	⊕⊕◯◯ LOW	Mean age: 7.5 yrs.
	3 mos.	1 RCT (Ruckley) N=36 (72 ears)	Air bone gap hearing levels were similar between TT and myringotomy ears at 3 months.	⊕⊕◯◯ LOW	Mean age: 5.1 yrs.
	6 mos.	2 RCTs (Popova, Vlastos) N=112	At 6 months, there was no difference in hearing levels between TT+Ad and myringotomy+Ad groups.	⊕⊕◯◯ LOW	Age: 4.5-5.1 yrs. (range of means)
	6 mos.	1 RCT (Black) N=37 (74 ears)	At 6 months f/u, there was no difference in mean hearing levels between TT and myringotomy ears in adenoidectomy patients.	⊕⊕◯◯ LOW	Mean age: 6.1 yrs.
	6 mos.	1 RCT (Shishegar) N=30 (60 ears)	Air bone gap hearing levels were similar between TT and myringotomy ears at 6 months.	⊕⊕◯◯ LOW	Mean age: NR (range, 4-8 yrs.)
	12 mos.	2 RCTs (Popova, Vlastos) N=109	At 12 months, mean hearing levels were similar between TT+Ad and myringotomy+Ad groups.	⊕⊕◯◯ LOW	Age: 4.5-5.1 yrs. (range of means)
	12 mos.	2 RCTs (Black, To) N=91 (182 ears)	At 12 months, there was no difference in mean hearing levels between TT and myringotomy ears in adenoidectomy patients.	⊕⊕◯◯ LOW	Age: 6.1-7.5 yrs. (range of means)
	12 mos.	1 RCT (To) N=108 (216 ears)	A similar proportion of TT and myringotomy ears in adenoidectomy patients had hearing levels that improved by more than 6 dB through 12 months.	⊕⊕◯◯ LOW	Mean age: 7.5 yrs.
	≤24 mos.	1 RCT (Gates) N=155	There was no difference in the percentage of patients with hearing loss (hearing levels ≥20 dB) between groups through 24 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
	24 mos.	1 RCT (Black) N=37 (74 ears)	At 24 months, there was no difference in mean hearing levels between TT and myringotomy ears in adenoidectomy patients.	⊕⊕◯◯ LOW	Mean age: 6.1 yrs.

Outcome	Follow-Up	Studies N	Comparative Impact: Hearing Levels	Quality	Age At Enrollment
TT+Ad Versus Ad For OME	6 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Brown) N=228 (457 ears)	At 6 months f/u, pooled results from three studies (N=173) (MD -3.72 dB (95% CI -5.8 to -1.7 dB, p=0.0004, I2=0%) as well as a fourth RCT (N=55) (MD ~-2.3 dB) suggest a modest benefit with TT. One trial (N=37) also reported significantly better air bone gap hearing levels in the ears randomized to TT at 6 months (14.5 vs. 20.4 dB, MD -5.9 dB, 95% CI -10.5 to -1.3 dB, p=0.0136). (All patients had bilateral OME and the majority had hearing loss at baseline.)	⊕⊕◯◯ LOW	Age: 5.9-6.1 yrs. (range of means in 2 RCTs); NR in 2 RCTs (range 2-10 yrs.)
	12 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Brown) N=252 (505 ears)	At 12 months f/u, there was no significant difference in mean hearing levels between groups.	⊕⊕◯◯ LOW	Age: 5.9-6.1 yrs. (range of means in 2 RCTs); NR in 2 RCTs (range 2-10 yrs.)
	24 mos.	2 RCTs (Black, Maw & Bawden) N=137 (275 ears)	At 24 months f/u, hearing levels were similar between groups. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Age: 3.9-6.0 yrs. (range of means in 2 RCTs); NR in 1 RCT (range 2-9 yrs.)
	36, 48, 84, 120 mos.	1 RCT (Maw & Bawden) N=42-112 (85-222 ears)	At 36, 48, 84, and 120 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: NR (range 2-9 yrs.)
	60 mos.	2 RCTs (Maw & Bawden, Brown) N=148 (297 ears)	At 60 months f/u, results were similar between groups. No firm conclusions can be made.	⊕⊕◯◯ INSUFFICIENT	Mean age: NR (range 2-10 yrs.)
TT Versus Myringotomy+Ad For OME	≤24 mos.	1 RCT (Gates) N=180	Through 24 months, there was no difference between groups in the percentage of appointments with hearing levels ≥20 dB in the better ear (10.1% vs. 7.8% of appointments, MD 2.3%, 95% CI -9.2% to 5.5%, p=0.1606). However, TT+Ad	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)

Outcome	Follow-Up	Studies N	Comparative Impact: Hearing Levels	Quality	Age At Enrollment
			patients had significantly more appointments with hearing levels in the worse ear that were 20 dB or higher (30.4% vs. 22.0% of appointments, MD 8.4%, 95% CI 2.9% to 13.9%, p=0.0028)		
TT Versus Ad For OME	6 mos.	2 RCTs (Dempster, Maw & Bawden) N=236	At 6 months, mean hearing levels were 3.45 dB better in the TT ear compared with the no treatment ear in adenoidectomy patients (pooled MD -3.45 dB, 95% CI -6.02 to -0.88 dB, p=0.008, I2=0%) in 2 RCTs.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.; NR in 1 RCT (range 2-9 yrs.)
	12 mos.	2 RCTs (Dempster, Maw & Bawden) N=236	At 12 months, mean hearing levels were similar between groups.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.; NR in 1 RCT (range 2-9 yrs.)
	24 mos.	1 RCT (Maw & Bawden) N=169	At 24 months f/u, hearing levels were similar between groups.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
	36 & 48 mos.	1 RCT (Maw & Bawden) N=155-169	Hearing levels were 2.1 to 2.8 dB worse in the TT ear at 36 months f/u (19.8 vs. 17.0 dB, MD 2.8 dB, 95% CI 0.1 to 5.5 dB, p=0.0428) and 48 months f/u (18.7 vs. 16.6 dB, MD 2.1 dB, 95% CI 0.6 to 3.6 dB, p=0.0066) in one RCT.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
	84 & 120 mos.	1 RCT (Maw & Bawden) N=58-102	At 84 and 120 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
TT Versus Antibiotics For OME	2 & 4 mos.	1 RCT (Bernard & Stenstrom) N=125	Mean hearing levels were significantly better in the TT group versus the antibiotics group at 2 months (~11 vs. ~20 dB, p<0.001) and 4 months (~12 vs. ~17 dB, p=0.0132). At both time points, significantly fewer TT patients had hearing levels greater than 25 dB versus antibiotics patients (no data reported).	⊕⊕◯◯ LOW	Mean age: 4.7 yrs.
	6, 12, & 18 mos.	1 RCT (Bernard & Stenstrom) N=125	There was no difference in mean hearing levels at 6, 12, and 18 months. The percentage of patients with hearing levels over 25 dB was statistically similar between groups (no data reported).	⊕⊕◯◯ LOW	Mean age: 4.7 yrs.

Outcome	Follow-Up	Studies N	Comparative Impact: Hearing Levels	Quality	Age At Enrollment
	72-120 mos.	Subanalysis of 1 RCT (Bernard & Stenstrom) N=113	Between 72 and 120 months follow-up, there was no significant difference between groups in mean hearing levels. No firm conclusions can be made.	⊕⊕◯◯ INSUFFICIENT	Mean age: 4.7 yrs.
TT Versus Antibiotics For AOM	≤24 mos.	1 RCT (Casselbrant 1992) N=163	Through 24 months, there was no difference between TT and antibiotics groups in the percentage of time spent with hearing levels above 15 dB.	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-2.9 yrs.)
TT Versus Placebo Or No Treatment For AOM	≤24 mos.	1 RCT (Casselbrant 1992) N=157	Through 24 months, TT patients spent 10% of the time with hearing levels above 15 dB in the better ear compared with 16% in the placebo group (95% CI NR, p-value NR).	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-2.9 yrs.)
TT (Unilateral) Versus Myringotomy Or No Treatment For AOM Or OME	3, 6, & 9 mos.	1 RCT (Le 1992) N=37 (74 ears)	Between 3 and 9 months follow-up, hearing levels were 3.4 to 3.7 dB better in the TT ear than the control ear: MD -3.4 dB at 3 months (95% CI -6 to -1 dB, p=0.02), MD -3.7 dB at 6 months (95% CI -7 to 0, p=0.05), MD -3.5 at 9 months (95% CI -6 to 0, p=0.02) in one RCT. Further, at 9 months, 32% of patients had hearing levels at least 5 dB lower in the TT ear (p=0.04).	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.
	12, 15, 18, 24, >24 mos.	1 RCT (Le 1992) N=37 (74 ears)	Between 12 and more than 24 months, hearing levels were statistically similar between groups. At 17 and 24 months, 14% to 28% of patients had had hearing levels at least 5 dB lower in the TT ear, although the difference was not statistically significant.	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.

*Hearing levels measured by audiometry unless otherwise indicated.

Speech and language development

***Summary*:** Speech and language outcomes were only evaluated for TT compared with watchful waiting for OME. There was no difference between groups at any time point evaluated.

Outcome	Follow-Up	Studies N	Comparative Impact: Speech And Language Development	Quality	Age At Enrollment
TT Versus WW For OME	6-9 mos.	3 RCTs (COMET, Rovers, Rach) N=393	At 6 to 9 months, verbal comprehension as measured by the Reynell test was similar between groups.	⊕⊕⊕◯ MODERATE	Age: 1.2-4.7 yrs. (range of means)
	6-9 mos.	3 RCTs (COMET, Rovers, Rach) N=393	Results at 6 to 9 months suggest no difference in expressive language between groups as measured by the Reynell and/or Schlichting tests.	⊕⊕◯◯ LOW	Age: 1.2-4.7 yrs. (range of means)
	12-18 mos.	2 RCTs (COMET, Rovers) N=388	At 12 to 18 months, there was no difference between groups in verbal comprehension as measured by the Reynell test.	⊕⊕⊕◯ MODERATE	Age: 1.2-2.9 yrs. (range of means)
	18 mos.	1 RCT (COMET) N=152	At 18 months, Reynell test expressive language scores were similar between groups.	⊕⊕⊕◯ MODERATE	Age: 1.2-2.9 yrs. (range of means)
	Age 3, 4, 6, 9-11 yrs.	1 RCT (Paradise) N=304-401	At age 3, 4, 6, or 9 to 11 years, there were no differences between groups in various measures of language development†.	⊕⊕⊕⊕ HIGH	Mean age: 1.25 yrs. (range 0.2-3 yrs.)
	Age 7-8 yrs.	1 RCT (COMET) N=67	At age 7 to 8 years, were no differences between groups in various measures of language development†.	⊕⊕◯◯ LOW	Mean age: 2.9 yrs. (range 1.2-4.7 yrs.)
All Other Comparators For OME		0 studies	No evidence	⊕◯◯◯ INSUFFICIENT	

Parent satisfaction

Summary: Parent satisfaction was reported in a subanalysis of one RCT that compared TT to antibiotics for OME; evidence was insufficient and thus no firm conclusions can be made.

Outcome	Follow-Up	Studies N	Comparative Impact: Parent Satisfaction	Quality	Age At Enrollment
TT Versus Antibiotics For OME	72-120 mos.	Subanalysis of 1 RCT (Bernard & Stenstrom) N=65	When measured between 72 and 120 months post-treatment, parent-reported treatment satisfaction was similar for children who received tubes only once versus those who never received tubes. No firm conclusions can be made.	⊕⊕◯◯ INSUFFICIENT	Mean age: 4.7 yrs.
All Other Comparators For OME Or AOM		0 studies	No evidence	⊕◯◯◯ INSUFFICIENT	

Patient quality of life

***Summary*:** While one trial of OME patients found no differences between groups in disease-specific patient quality of life at 6 or 12 months, another small RCT of obstructive sleep apnea patients with OME reported greater improvement in disease-specific patient quality of life at 6 months, although the difference was not sustained at 12 months. A subanalysis of one RCT comparing TT to no treatment for AOM found no differences between groups at 4 or 12 months.

Outcome	Follow-Up	Studies N	Comparative Impact: Patient Quality Of Life	Quality	Age At Enrollment
TT Versus WW For OME	6 & 12 mos.	1 RCT (Rovers) N=165-176	There were no significant differences between groups at 6 or 12 months f/u in any subdomain of the TAIQOL.	⊕⊕⊕◯ MODERATE	Mean age: 1.6 yrs.
TT+Ad Versus Myringotomy+Ad For OME	6 mos.	1 RCT (Vlastos, sleep apnea patients) N=44	At 6 months, TT+Ad-Tons patients had significantly greater improvement (from baseline) in disease-specific quality of life scores (OM-6) compared with myringotomy+Ad-Tons patients (-0.38 vs. 0.00, MD -0.38, 95% CI -0.64 to -0.12, p=0.0050).	⊕⊕◯◯ LOW	Mean age: 4.5 yrs.
	12 mos.	1 RCT (Vlastos, sleep apnea patients) N=41	At 12 months, improvement in OM-6 scores from baseline was similar between groups.	⊕⊕◯◯ LOW	Mean age: 4.5 yrs.
TT Versus No Treatment For AOM	4 & 12 mos.	Subanalysis of 1 RCT (Kujala) N=81-85	There were no differences between treatment groups in ear-related quality of life.	⊕⊕◯◯ LOW	Mean age: 3.6 yrs.
All Other Comparators For OME Or AOM		0 studies	No evidence	⊕◯◯◯ INSUFFICIENT	

Cholesteatoma

***Summary*:** There was no difference between groups in the incidence of cholesteatoma at any time point measured.

Outcome	Follow-Up	Studies N	Comparative Impact: Cholesteatoma	Quality	Age At Enrollment
TT Versus WW For OME	≤36 mos. & At age 5	2 RCTs (Paradise, Mandel 1989) N=275	There was no difference between groups in either trial.	⊕⊕◯◯ LOW	Mean age: 1.25 yrs. in 1 RCT, NR by 1 RCT (range 0.6-12 yrs.)
TT Versus Myringotomy For OME	≤24-36 mos.	2 RCTs (Gates, Mandel 1992) N=353	There was no difference between groups for this relatively rare outcome.	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-12 yrs.)
TT+Ad Versus Myringotomy+Ad For OME	≤24 mos.	1 RCT (Gates) N=301	There were no cases of cholesteatoma in either group through 24 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
TT+Ad Versus Ad For OME	60 mos.	1 RCT (Brown) N=55 (110 ears)	One trial reported no cases of cholesteatoma at 60 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-10 yrs.)
TT Versus Myringotomy+Ad For OME	≤24 mos.	1 RCT (Gates) N=301	There were no instances of cholesteatoma in either group through 24 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
TT Versus Antibiotics For AOM	≤24-30 mos.	2 RCTs (Casselbrant 1992, Gebhart) N=258	There were no cholesteatomas in either group through 24 or 30 months.	⊕⊕◯◯ LOW	Mean age: 1.7 yrs. NR by 1 RCT (range 0.6-2.9 yrs.)
TT Versus Placebo Or No Treatment For AOM	≤24 mos.	1 RCT (Casselbrant 1992) N=163	There were no cholesteatomas in either group through 24 months in one RCT.	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-2.9 yrs.)
TT (Unilateral) Versus Myringotomy Or No Treatment For AOM Or OME	≤24 mos.	1 RCT (Le) N=57 (114 ears)	There were no cholesteatomas in either group through 24 months in one RCT.	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.

Outcome	Follow-Up	Studies N	Comparative Impact: Cholesteatoma	Quality	Age At Enrollment
All Other Comparators For OME		0 studies	No evidence	⊕◯◯◯ INSUFFICIENT	

Perforation

***Summary*:** There was no difference between groups in formation of persistent perforation.

Outcome	Follow-Up	Studies N	Comparative Impact: Perforation	Quality	Age At Enrollment
TT Versus WW For OME	≤24-36 mos.	3 RCTs (TARGET, Mandel 1989, Mandel 1992) N=169 & 635 ears	No comparative data were provided. One trial reported perforation in 1.3% of tubed ears; two RCTs reported that perforation occurred in 11.2% to 13.7% of all patients (including TT, WW, and myringotomy), but did not separate results out by treatment group. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 5.2 yrs. in one trial, NR in 2 trials (range 0.6-12 yrs.)
TT (Unilateral) Versus No Treatment (Contralateral) For OME	6-60 mos.	2 RCTs (Dempster, Lildholdt) N=169 (204 ears)	Perforation or attic retraction occurred similarly between groups.	⊕⊕◯◯ LOW	Age: 3.9-5.7 yrs. (range of means)
TT Versus Myringotomy For OME	≤24-36 mos.	3 RCTs (Gates, Mandel 1989, Mandel 1992) N=660	Persistent perforation occurred similarly between tubed and myringotomy patients. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range 0.6-12 yrs.)
TT+Ad Versus Myringotomy+Ad For OME	≤24-36 mos.	3 RCTs (Casselbrant, Gates, Ruckley) N=591	Persistent perforation was relatively uncommon and occurred similarly between groups.	⊕⊕◯◯ LOW	Mean age: 2.9-5.1 in 2 RCT, NR by 1 RCT (range 4-8 yrs.)
TT+Ad Versus Ad For OME	60 mos.	1 RCT (Brown) N=55 (70 ears)	There were no cases of perforation at 60 months in either ear.	⊕⊕◯◯ LOW	Mean age: NR (range 4-10 yrs.)
TT Versus Myringotomy+Ad For OME	≤24 & 36 mos.	2 RCTs (Gates, Casselbrant) N=557	Persistent perforation occurred similarly between groups.	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
TT Versus Ad For OME	6 & 12 mos.	1 RCT (Dempster) N=72	Perforation or retraction occurred similarly in both ears through 6 and 12 months.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.

Outcome	Follow-Up	Studies N	Comparative Impact: Perforation	Quality	Age At Enrollment
TT Versus Antibiotics For OME	≤18 mos.	1 RCT (Bernard & Stenstrom) N=60	There were no chronic perforations in the TT group (n=60) through 18 months. The composite outcome of perforation, retraction, or atelectasis was more common in the TT group than the antibiotics group as randomized (RR 1.5, 95% CI 1-2 to 1.9) or as treated (i.e., those who received tubes versus those who never received tubes) (RR 4.8, 95% CI 2.2 to 10.6).	⊕⊕◯◯ LOW	Mean age: 4.9 yrs.
TT Versus Antibiotics For AOM	≤21 mos.	2 RCTs (Casselbrant 1992, Gebhart) N=130	Perforation occurred in 3.7% TT patients (2/54) in one trial and healed by 9 months; another trial reported perforations in 13.2% of TT patients (10/76); of these 7 healed spontaneously within a few months and the remainder persisted for 5, 9, and 21 months but eventually healed spontaneously.	⊕⊕◯◯ LOW	Mean age: 1.7 yrs. NR by 1 RCT (range 0.6-2.9 yrs.)
TT Versus Placebo Or No Treatment For AOM	≤21 mos.	1 RCT (Casselbrant 1992) N=76	Perforation occurred in 13.2% of TT patients (10/76); of these 7 healed spontaneously within a few months and the remainder persisted for 5, 9, and 21 months but eventually healed spontaneously.	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-2.9 yrs.)
TT (Unilateral) Versus Myringotomy Or No Treatment For AOM Or OME	≤24 mos.	1 RCT (Le) N=57 (114 ears)	Permanent perforation occurred in 4% of TT ears and no control ears through 24 months.	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.

Chronic otorrhea

***Summary*:** Results were mixed, with chronic otorrhea (occurring three or more times a year) more common following TT compared with watchful waiting through 12 months in one trial but occurred similarly between TT + adenoidectomy and myringotomy + adenoidectomy groups through 12 months in another trial. There was no difference between TT and WW or myringotomy groups in the development of persistent otorrhea requiring hospitalization based on data from two RCTs.

Outcome	Follow-Up	Studies N	Comparative Impact: Chronic Otorrhea	Quality	Age At Enrollment
TT Versus WW For OME	≤12 mos.	1 RCT (Rovers) N=187	Otorrhea that occurred three or more times within 12 months following treatment (i.e., chronic otorrhea) was significantly more common in the TT group compared with the WW group (25% vs. 5%, RD 19%, 95% CI 10% to 29%, p<0.01).	⊕⊕◯◯ LOW	Mean age: 1.6 yrs.
	≤36 mos.	2 RCTs (Mandel 1989, Mandel 1992) N=89	Persistent otorrhea requiring hospitalization, intravenous antibiotics, and daily suctioning occurred similarly between groups.	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-12 yrs.)
TT Versus Myringotomy For OME	≤36 mos.	2 RCTs (Mandel 1989, Mandel 1992) N=89	Persistent otorrhea requiring hospitalization, intravenous antibiotics, and daily suctioning occurred similarly in the TT and myringotomy groups. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range 0.6-12 yrs.)
TT+Ad Versus Myringotomy+Ad For OME	≤12 mos.	1 RCT (Popova) N=78	Chronic otorrhea (≥3 episodes per year) occurred similarly between groups through 12 months.	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-12 yrs.)
All Other Comparators For OME Or AOM		0 studies	No evidence	⊕◯◯◯ INSUFFICIENT	

Differential efficacy or safety in subgroups

Summary: No firm conclusions can be made due to insufficient quality evidence.

Outcome	Follow-up	Studies N	Conclusions: HTE	Quality	Age at enrollment
TT versus WW for OME	6 mos.	1 RCT (Rovers) N=206	One trial found that baseline hearing levels significantly modified the effect of hearing improvement at 6 months such that patients with worse baseline hearing improved more following TT (versus WW) than those with better baseline hearing following (p=0.023 for the better ear, p=0.04 for the worse ear). No other exposures tested (history of adenoidectomy, season at randomization, number of upper respiratory tract infections since birth, hospital) modified this outcome; no data were reported. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 1.6 yrs.
	6, 12 mos.	1 RCT (Rovers) N=206	One trial found that no exposures tested (baseline hearing level, history of adenoidectomy, season at randomization, number of upper respiratory tract infections since birth, hospital) modified quality of life as measured by the TAIQOL measure at 6 or 12 months; no data were reported. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 1.6 yrs.
TT (unilateral) versus no treatment (contralateral) for OME	6 & 12 mos.	1 RCT (Dempster) N=35 (70 ears)	One trial reported improvements in hearing levels at 6 and 12 months separately for boys versus girls by treatment group, although no formal test for interaction was performed. At six months, while boys and girls in the TT ear had similar improvements in hearing levels, boys in the untreated ear had less improvement than girls in the untreated ear. At 12 months, hearing improvement was similar across both genders and both treatment groups, suggesting no effect modification. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 5.7 yrs.
TT versus Myringotomy for OME	≤24 mos.	1 RCT (Gates) N=177	One trial conducted a test for interaction to evaluate whether any prespecified baseline characteristics modified the outcomes of time with effusion as well as time to recurrence. No interaction was found between the group, outcomes, and any characteristic tested (age, sex, ethnic	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range 4-8 yrs.)

Outcome	Follow-up	Studies N	Conclusions: HTE	Quality	Age at enrollment
			group, laterality of effusion, referral source), however no details or data were reported. No firm conclusions can be made.		
TT+Ad versus Myringotomy+Ad for OME	≤24 mos.	1 RCT (Gates) N=301	Gates conducted a test for interaction to evaluate whether any prespecified baseline characteristics modified the outcomes of time with effusion as well as time to recurrence. No interaction was found between the group, outcomes, and any characteristic tested (age, sex, ethnic group, laterality of effusion, referral source), however no details or data were reported. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range, 4-8 yrs.)
TT+Ad versus Ad for OME	6 & 12 mos.	1 RCT (Dempster) N=35 (70 ears)	One trial reported improvements in hearing levels at 6 and 12 months stratified by treatment and gender, although no formal test for interaction was performed. At both 6 and 12 months, hearing improvement was similar across both genders and both treatment groups, suggesting no effect modification. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 5.9 yrs.
All other comparators for OME or AOM		0 studies	No evidence	⊕◯◯◯ INSUFFICIENT	

Cost effectiveness: One cost-utility analysis evaluated costs alongside a RCT (Rovers[29,65-67]) of 187 children (mean age 19.4 months) with persistent bilateral OME and hearing loss treated with TT versus WW. Outcomes assessed were language development and time without effusion through 1 year. The analysis was conducted from a societal perspective; both direct and indirect costs were included (using 1998 dollars). The study was reasonably well conducted (QHES score = 80/100). The results of the trial indicated that by 1 year there were no statistically significant differences in comprehensive or expressive language as measured by the Reynell test and the Schlichting test between the two groups, even though the mean duration of OME for those treated conservatively was 4.5 months longer than those treated with TT. In terms of cost, tube insertion was more expensive with a mean total cost per child of $454 versus $120 with watchful waiting (p<0.001). According to the sensitivity analysis, the incremental costs of TT insertion varied between $320 and $491 depending on the cost of the surgery (including day care and 3 visits to an ENT specialist) and the cost of an additional ENT visit. Non-medical costs were low in both groups. ICERs could not be calculated since no differences in language development were found; however, estimated ICERs were calculated using the bootstrapping technique which indicated higher costs for TT with no differences in effect. Based on these results, the authors recommend that insertion of TT should not be a standard treatment in all children with persistent OME.

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1. Appraisal

1.1. Rationale

Middle ear inflammation (otitis media) is one of the most common ailments of childhood, with a diagnostic frequency second only to upper respiratory infection. Otitis media can present as an ear infection (acute otitis media) or as fluid in the middle ear in the absence of an infection (otitis media with effusion). In some children, ear infections do not respond to antibiotic therapy or recur within a month of completing antibiotics (persistent otitis media) or continue to recur within six to twelve months (recurrent otitis media). Persistent or recurrent otitis media as well as chronic otitis media with effusion can lead to long-term hearing problems, frequent doctor visits, decreased quality of life for both the child and parent, as well as missed school and work. Further, hearing loss can lead to a number of developmental delays, including speech, language, and cognitive problems, the impact of which are likely even greater in children already at risk for developmental difficulties or delays (including those with conditions such as autism spectrum disorders, Down syndrome, among others).

Tympanostomy tube insertion is the primary surgical treatment for otitis media with or without effusion, and is performed in approximately 667,000 children each year. Tympanostomy tubes are small tubes that are inserted into the eardrum in order to allow the flow of both air and fluid between the middle and outer ear. Tube placement is performed under general anesthesia, and tubes typically fall out within 12 to 14 months. Tympanostomy tubes may decrease the occurrence of otitis media, and may improve hearing and quality of life. Risks of tympanostomy tube insertion may include otorrhea, blockage of the tube lumen, granulation tissue formation, premature tube extrusion, and tube displacement. In addition, there are risks associated with use of general anesthesia. In the longer term, tympanostomy tubes may lead to changes in the eardrum as well as possible long-term hearing loss. Other treatment options include antibiotics or other medications such as steroids or mucolytics, myringotomy (eardrum incision), adenoidectomy, or autoinflation of the Eustachian tube. In addition, because otitis media often resolves spontaneously, especially within the first six months, and may not cause long-term hearing or developmental problems, watchful waiting or delayed tube placement may be considered.

Policy Context

There are significant questions related to the use of tympanostomy tubes for the treatment of otitis media with effusion in children under the age of 16 regarding efficacy, safety, differential efficacy and safety in subgroups, and cost.

Objectives

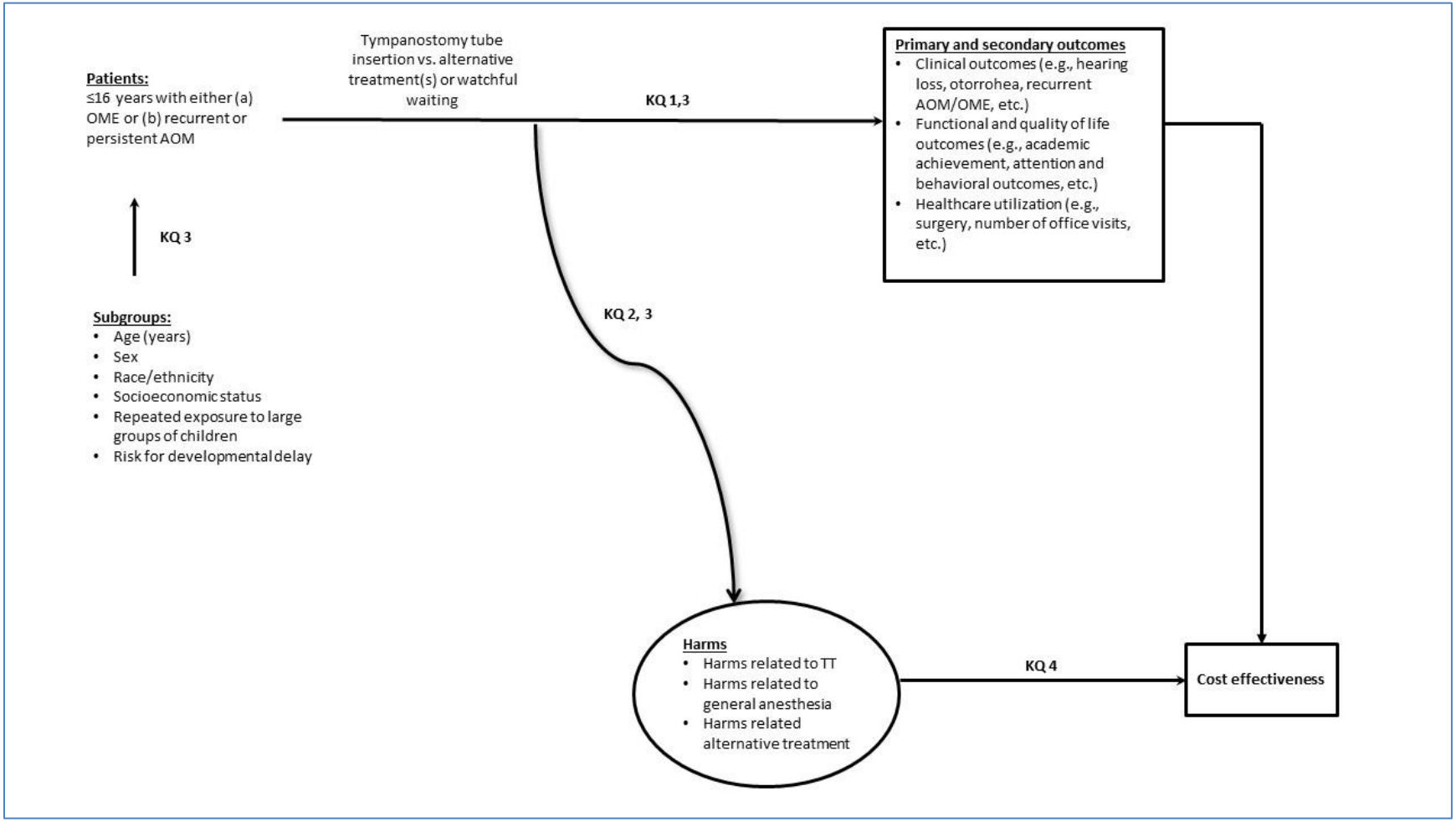
To systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of tympanostomy tubes in children for treating otitis media with or without effusion. The differential effectiveness and safety of tympanostomy tubes for subpopulations will be evaluated, as will the cost effectiveness.

1.2. Key Questions

In children aged 16 years and younger with either (a) chronic otitis media with effusion (OME) or (b) recurrent or persistent acute otitis media (AOM) (evaluated separately):

1. What is the evidence of the short- and long-term efficacy and effectiveness of tympanostomy tube insertion compared with alternative treatment options or watchful waiting? Under what circumstances are tympanostomy tubes indicated?
2. What is the evidence regarding short- and long-term harms and complications of placement of tympanostomy tubes compared with alternative treatment options or watchful waiting?
3. Is there evidence of differential efficacy, effectiveness, or safety of tympanostomy tubes compared with alternative treatment options or watchful waiting? Include consideration of age, sex, race, ethnicity, socioeconomic status, risk for developmental delay, repeated exposure to large groups of children, duration of otitis media, and recurrent acute versus chronic otitis media.
4. What is the evidence of cost-effectiveness of tympanostomy tubes compared with alternative treatment options?

Figure 1. Analytic framework



1.3. Outcomes Assessed

Hearing
Hearing levels are measured in the logarithmic unity of decibels (dB). Normal hearing levels in children range from 0 to 20 dB; hearing levels of 41 to 55 dB indicate mild hearing loss, 56 to 70 dB indicate moderate to severe hearing loss, and 71 or higher indicates severe hearing loss. For context, soft speech is typically 30 dB, while normal speech is around 50 dB.[138] Hearing levels were most commonly evaluated in the included studies using pure tone audiometry. During this test, sounds at varying frequencies (e.g., 500, 100, 2000, and 4000 Hz) and intensity are played at into headphones and the child is asked indicate when a sound is heard. The lowest level of sound, which is measured in decibels (dB), the child can repeatedly detect is the hearing level; typically the hearing level reflects the average of all tested frequencies. No studies were identified that evaluated the minimal clinically important difference in hearing levels; one of the clinical experts indicated that returning hearing to normal levels (≤20 dB) was of primary importance.

A list of the outcome measures used in studies included in this report is provided in Table 1.

Table 1. Outcome measures used in included studies

Outcome Measure	Assessed by	Components	Score Range	Interpretation
Academic Achievement Outcome Measures				
Oral reading fluency test[39]	Teacher	The number of words in a grade-level passage read correctly in 1 minute.	0 to variable maximum	The higher the score, the lower the reading impairment.
SATS Key Stage 1[156]	Teacher	2 subscales (variable number of items): • English concepts • Math concepts	Variable point thresholds depending on number of items	The lower the score, the greater the academic impairment. Level 1: Below expectations Level 2: At level expected Level 3: Beyond expectations Level 4: Exceptional
Woodcock-Johnson III Tests of Achievement: Standard Battery[147]	Parent, teacher	22 subscales: • Verbal comprehension • Visual-auditory learning • Spatial relations • Sound blending • Concept formation • Visual matching • Numbers reversed • Incomplete words	Normative mean score is 100 ± 15	The higher the score, the lower the academic impairment.

Outcome Measure	Assessed by	Components	Score Range	Interpretation
		• Letter-word identification • Reading fluency • Story recall • Understanding directions • Calculation • Math fluency • Spelling • Writing fluency • Passage comprehension • Applied problems • Writing samples • Story recall-delayed The number of correct responses is counted.		
Woodcock-Johnson III: Reading Mastery Tests (Revised normative updated version)[31]	Parent, teacher	6 subscales: • Visual-auditory learning • Letter identification • Word identification • Word attacks • Word comprehension • Passage comprehension The number of correct responses is counted. For visual-auditory learning subscale, number of errors is counted.	Normative mean score is 100 ± 15	The higher the score, the lower the reading impairment.
UK local school entry tests ([58] as cited in COMET trial)	Teacher	4 subscales: • Language • Reading • Writing • Math	Scores indicate various stages of performance ranging from stage 2 to 7.	The higher the score, the lower the academic impairment. Stage 2 scores: least advanced Stage 7 scores: most advanced
Attention and Behavioral Outcome Measures				
Child Behavior Checklist (CBCL)[29]	Parent, teacher	8 subscales (113 items): • Anxious/ depressed • Depressed • Somatic complaints • Social problems	Normative mean T score is 50 ± 10 for each scale and Total Problems	The higher the score, the greater the behavioral impairment.

Outcome Measure	Assessed by	Components	Score Range	Interpretation
		• Thought problems • Attention problems • Rule-breaking behavior • Aggressive behavior Each item has a minimum score of 0 and a maximum score of 2.		
Children's Disruptive Behavior Disorders Rating scale[120]	Parent, teacher	1 subscale (36 items): • DSM-III-R diagnostic criteria for ADHD, ODD, and CD Each item has a minimum score of 0 and a maximum score of 3.	0 to 108	The higher the score, the greater the behavioral impairment.
Impairment rating scales[46]	Parent, teacher	6 or 7 subscales depending on version (5 items): • Relationship with peers • Relationship with siblings (absent in teacher version) • Relationship with parents/ teacher • Academic progress • Self-esteem • Influence on family/ classroom functioning • Overall impairment Each item has a minimum score of 0 and a maximum score of 6.	0 to 30	The higher the score, the greater the behavioral impairment. Score ≥3: clinically meaningful impairment
Richman Behavior Checklist[131]	Clinician	1 subscale (12 items): • Behavior – most common reasons for attendance at psychiatric clinics in this age group Each item has a minimum score of 0 and a maximum score of 2.	0 to 24	The higher the score, the greater the behavioral impairment. Score ≥ 11: disturbed
Social Skills Rating System (SSRS)[33]	Parent, teacher	3 subscales (34-57 items): • Social skills • Problem behaviors • Academic competence Each item has a minimum score of 0 and a maximum score of 2.	0 to 114 Normative mean score is 100 ± 15	The higher the score, the lower the social impairment.
Strengths and	Parent,	5 subscales (25 items):	0 to 40	The higher the score,

Outcome Measure	Assessed by	Components	Score Range	Interpretation
Difficulties Questionnaire (SDQ)[56]	teacher	• Emotional symptoms • Conduct problems • Hyperactivity/ inattention • Peer relationship problems • Prosocial behavior Each item has a minimum score of 0 and a maximum score of 2. Items 7, 11, 14, 21, and 35 are scored inversely.		the greater the behavioral impairment. Score 0-13 (parent) or 0-11 (teacher): close to average Score 14-16 (parent) or 12-15 (teacher): slightly raised Score 17-19 (parent) or 16-18 (teacher): high Score 20-40 (parent) or 19-40 (teacher): very high
Continuous Performance test (CPT)[8] • Auditory • Visual	Clinician	2 subscales (1080 items: one task presented at a rate of 1 per second over a 9-minute span; = 540 per task, and 1080 total): • Visual • Auditory The number of correct, incorrect, and omitted responses for each subscale is recorded.	0 to 1080	The higher the score, the lower the attention impairment.
Auditory Processing				
Hearing in Noise Test (children's version)[112]	Clinician	1 subscale (21 items): • Sentences are played at 65 dB from speakers at 0 degrees, 90 degrees to the left, and 90 degrees to the right of the child. Seven different sentences are presented at each speaker location. The loudness of the speaker is increased until the child can hear and repeat the sentence. 65 dB is subtracted from the average loudness (in decibels) at each speaker location required for the child to complete the task.	NA	The higher the score, the greater the auditory impairment.
SCAN Screening Test for Auditory Processing	Clinician	4 subscales (120 items): • Filtered words	0 to 120	The higher the score, the lower the

Outcome Measure	Assessed by	Components	Score Range	Interpretation
Disorders[72]		• Auditory figure-ground • Competing words • Competing sentences The number of correct responses is counted.	Normative mean score is 100 ± 15	auditory impairment.
Speech-in-noise McCormick Automated Toy Test[96]	Clinician	Determines minimum sound threshold at which a child can identify presented words.	Not applicable	The higher the score, the lower the auditory impairment.
Patient and Parent Interaction				
Erikson Child-Parent Interaction[44]	Clinician	3 subscales (17 items): • Conferenced observations • Preschool behavior questionnaire • Behavior-problem scale Each item has a minimum score of 0 and a variable maximum score of 3 to 7.	Each subscale scored separately.	The higher the score, the better the interaction.
Parenting Stress Index, Short-Form (PSI/SF)[3]	Parent	3 subscales (36 items): • Parental distress • Parent-child dysfunctional interaction • Difficult child Each item has a minimum score of 1 and a maximum score of 5.	<u>Normative mean scores</u> Parental Stress: 26±7 Parent–Child Dysfunctional Interaction: 19±5 Difficult Child: 26±7 Total Stress score: 71±15	The higher the score, the greater the parental stress.
Quality of Life				
Otitis Media-6 (OM-6) (disease-specific)[136]	Clinician	6 subscales (6 items): • Physical suffering • Hearing loss • Speech impairment • Activity limitations • Emotional distress • Caregiver concern Each item has a minimum score of 1 and a maximum score of 7.	Score adjusted to a scale of 1 to 7, by totaling the items' scores and dividing total by 6.	The higher the score, the lower the quality of life.
TAIQOL (TNO-AZL Infant Quality of Life) ([157] as cited by Rovers	Parent	13 subscales (46 items): • Lungs	0 to 100	The higher the score, the lower the quality of life.

Outcome Measure	Assessed by	Components	Score Range	Interpretation
trial)		• Stomach • Skin • Sleeping • Appetite • Eating problems • Aggressive behavior • Positive emotions • Emotions of panic • Vitality • Social behavior • Motoric problems • Communications Each item has a minimum score of 0 and a variable maximum score.		
Speech and Language				
Children's Nonword Repetitive Task[42]	Clinician	In standardized phonological strings of increasing length (1, 2, 3, and 4 syllables), the percentage of phonemes repeated correctly is calculated.	0 to 100%	The higher the score, the lower the language impairment. Score ≤70%: LR 25.15 of being language impaired Score 71-74%: LR 3.11 of being language impaired Score 75-80%: LR 0.62 of being language impaired Score ≥81%: LR 0.03 of being language impaired
Schlichting Test ([146] as cited by Rovers trial)	Parent, clinician	4 subtests (425 items): • Sentence development • Vocabulary test • Auditory memory • Parent-reported vocabulary checklist The number of correct responses is counted.	Normative mean score of 100 ± 15	The higher the score, the lower the language impairment.
Comprehensive Tests of Phonological	Clinician	Elision subtest - 20 items • Measures extent to which	0 to 20 or 72, depending on	The higher the score, the lower the

Outcome Measure	Assessed by	Components	Score Range	Interpretation
Processing (CTOPP)[103] • Elision subtest • Rapid letter naming subtest		an individual can say a word and then say what is left after dropping certain sounds Rapid letter naming subtest - 72 items • Measures speed at which an individual can name the letters on two pages The number of correct answers is counted.	subtest Normative mean standard score for subtests is 10 ± 3	language impairment.
Peabody Picture Vocabulary Test-revised (PPVT-R) ([167] as cited in Paradise trial)	Clinician	175 "stimulus words" are presented, and the child must correctly identify the corresponding image from a presented 4-panel black and white "image plate". Basal: the last item in the highest series of 8 consecutive correct responses Ceiling: the last item in the lowest series of 8 consecutive items with 6 incorrect responses Raw score: the number of correct responses below the ceiling; calculated by subtracting the errors between the highest basal and lowest ceiling from the item number of the lowest ceiling.	Normative mean score is 100 ± 15	The higher the score, the lower the language impairment.
Reynell Developmental Language Scales (RDLS), expressive language ([130] as cited in COMET trial)	Clinician	3 subscales (67 items): • Syntax • Vocabulary • Content	Standardized scores ranging from -3.1 to 3.1, where 0 = age-appropriate performance.	The higher the score, the lower the language impairment.
Wechsler Objective Language Dimensions (WOLD) ([144] as cited in COMET trial)	Clinician	2 subscales • Oral expression • Listening comprehension Raw score calculated as sum of items the child got correct.	Unclear	The higher the score, the lower the language impairment.

1.4. Washington State utilization and cost data

PUBLIC EMPLOYEE BENEFITS (PEBB)

Utilization: Tympanostomy Tube Procedures (Procs) January 2013 thru March 2015

CPT Codes: 69436, 69433[1]

Members 0 - 17 years old; N = 356

PEBB 2013 - 2015 (3 months)

Year	Mbrs/ Procs	Ct: Mbrs w/>=2 Procs/ annum	Total Procedures (Procs)	Total Mbrs 0-17	Procs/ 1,000	Paid$	Avg Pd$/Proc
2013	154	6	160	41,347	3.9	$667,503	*$4,172*
2014	184	4	188	42,584	4.4	$707,431	*$3,763*
2015	45	0	45	39,520		$163,618	*$3,636*
Overall	383		393			$1,538,551	*$3,915*

*** Mutually exclusive by year; not between years*

Paid dollars are calculated by capturing all claims for day of service.

MEDICAID

Utilization: Tympanostomy Tube Placement January 2012 thru April 2015

CPT Codes: 69436, 69433

Members 0 - 17 years old; N = 10,694

MEDICAID 2012 - 2015 (4 MONTHS)

Year	Mbrs w/ Procs	Ct: Mbrs w/>=2 Procs/ annum	Total Procedures (Procs)	Total Mbrs 0-17	Procs/ 1,000	Paid$	*Avg Pd$/Proc*
2012	3,498	125	3,627	827,402	4.2	$5,897,191	*$1,624*
2013	3,654	127	3,790	838,042	4.4	$5,993,014	*$1,579*
2014	3,418	120	3,539	869,200	3.9	$5,617,530	*$1,586*

[1] **69433** Tympanostomy requiring insertion of ventilating tube, local or topical anesthesia; for bilateral procedure report 69433 w/modifier 50.

69436 Tympanostomy requiring insertion of ventilating tube, general anesthesia; for bilateral procedure, report 69436 w/ modifier 50).

PUBLIC EMPLOYEE BENEFITS (PEBB)

Count and Distribution of Tympanostomy Tube Procedures by Age Group
January 2013 thru March 2015
CPT Codes: 69436, 69433; Members 0 - 17 years old

PEBB 2013 - 2015 (3 months)

	2013		2014		2015	
Age Grp	Proc	Dist	Proc	Dist	Proc	Dist
<1	11	7%	19	10%	4	9%
01-04	**99**	**62%**	**115**	**61%**	**30**	**67%**
05-09	41	26%	46	24%	10	22%
10-12	7	4%	5	3%	1	2%
13-14	2	1%	1	1%		0%
15-17		0%	2	1%		0%
Grand Total	**160**	**100%**	**188**	**100%**	**45**	**100%**

MEDICAID

Count and Distribution of Tympanostomy Tube Procedures by Age Group
January 2012 thru April 2015
CPT Codes: 69436, 69433; Members 0 - 17 years old

	2012		2013		2014	
Age Grp	Proc	Dist	Proc	Dist	Proc	Dist
<1	286	8%	303	8%	267	8%
1 - 4	**2,279**	**63%**	**2,316**	**61%**	**2,121**	**60%**
5 - 9	798	22%	887	23%	871	25%
10 - 12	165	5%	169	4%	160	5%
13 - 14	66	2%	61	2%	65	2%
15 - 17	32	1%	54	1%	56	2%
Grand Total	**3,626**	**100%**	**3,790**	**100%**	**3,540**	**100%**

PUBLIC EMPLOYEE BENEFITS (PEBB)

Count and Distribution of Single and Double[2] Tympanostomy Tube Procedures

January 2013 thru March 2015

CPT Codes: 69436, 69433; Members 0 - 17 years old

PEBB 2013 - 2015 (3 Months)

Type	2013		2014		2015	
	Proc	Dist	Proc	Dist	Proc	Dist
Double	138	86%	166	88%	31	69%
Single	8	5%	9	5%	7	16%
Unknown	14	9%	13	7%	7	16%
Grand Total	160	100%	188	100%	45	100%

MEDICAID

Count and Distribution of Single and Double[3] Tympanostomy Tube Procedures

January 2012 thru April 2015

CPT Codes: 69436, 69433; Members 0 - 17 years old

	2012		2013		2014	
	Procs	Dist	Procs	Dist	Procs	Dist
Double	3,098	85.41%	3,255	85.88%	3,233	91.33%
Single	336	9.26%	367	9.68%	240	6.78%
Multiple Procedure	30	0.83%	36	0.95%	12	0.34%
Unknown	163	4.49%	132	3.48%	55	1.55%
Grand Total	3,627	100%	3,790	100%	3,540	100%

PUBLIC EMPLOYEE BENEFITS (PEBB)

[2] Double procedures are indicated by use of Modifier 50 with either 69436 or 69433.

[3] Double procedures are indicated by use of Modifier 50 with either 69436 or 69433.

Count and Distribution of Top Ten Primary ICD-9 Dx Codes as Reason for Procedure
January 2013 thru March 2015

CPT Codes: 69436, 69433; Members 0 - 17 years old

Diagnosis	2013		2014		2015		Overall	
	Procs	Dist	Procs	Dist	Procs	Dist		
OTITIS MEDIA NOS	71	31%	60	23%	20	32%	151	27%
CHR SEROUS OM SIMP/NOS	43	19%	40	15%	13	21%	96	17%
DYSFUNCT EUSTACHIAN TUBE	27	12%	51	20%	7	11%	85	15%
CHR NONSUP OM NOS/NEC	28	12%	35	13%	9	14%	72	13%
HYPERTROPHY ADENOIDS	22	10%	24	9%	7	11%	53	10%
HYPERTROPHY T AND A	11	5%	17	7%	2	3%	30	5%
CHR MUCOID OM SIMP/NOS	9	4%	10	4%	2	3%	21	4%
AC NONSUP OTITIS MED NOS	3	1%	12	5%		0%	15	3%
NONSUPP OTITIS MEDIA NOS	6	3%	6	2%	2	3%	14	3%
CHR TUBOTYMPAN SUPPUR OM	7	3%	6	2%	1	2%	14	3%
Grand Total	227	100%	261	100%	63	100%	551	100%
Grand Total All Procedures for Year	383		459		109		951	
Top 10 Procs Account for	83%		87%		58%		84%	

MEDICAID

Count and Distribution of Top Ten Primary ICD-9 Dx Codes as Reason for Procedure

January 2012 thru April 2015

CPT Codes: 69436, 69433; Members 0 - 17 years old

	2012		2013		2014		2015	
Diagnosis	Procs	Dist	Procs	Dist	Procs	Dist	Procs	Dist
Dysfunct eustachian tube	954	29%	895	26%	874	28%	351	27%
Chr serous OM simp/NOS	944	28%	966	28%	743	24%	330	25%
Otitis media NOS	471	14%	549	16%	534	17%	215	16%
Chr nonsup OM NOS/NEC	397	12%	461	13%	461	15%	172	13%
Chr mucoid OM simp/NOS	150	5%	157	5%	132	4%	44	3%
Hypertrophy T and A	114	3%	114	3%	114	4%	36	3%
Nonsupp otitis media NOS	79	2%	101	3%	112	4%	66	5%
Chr sup otitis media NOS	71	2%	72	2%	83	3%	45	3%
Hypertrophy adenoids	66	2%	64	2%	69	2%	25	2%
Ac nonsup otitis med NOS	87	3%	66	2%	38	1%	25	0
Grand Total	3,333	100%	3,445	100%	3,160	100%	1,309	1
Top 10 DX account for	92%		91%		89%		89%	

2. Background

2.1. Epidemiology and Burden of disease

Middle ear inflammation, also known as otitis media (OM), is one of the most common childhood ailments, with a diagnostic frequency second only to upper respiratory infection.[138] It is estimated that by age one, 62% of children will have had at least one episode of OM.[30] OM often spontaneously resolves, but approximately 46% of children will have more than three episodes of OM with effusion (OME) by age 3.[30] As such, the short-term and long-term effects are significant due to the high prevalence of OM in the population.[17,32,40,52,55,79,86,89,97,106,126,153,155,159,161,175,176]

There is concern that OM—particularly long-term, persistent OM— reduces quality of life, incurs great economic costs, and impedes child development. OM can lead to fever and ear ache (otalgia), which can severely affect the quality of life (QoL) for both children and parents, resulting not only in physical and emotional discomfort for all involved, but also in missed days of school, missed days of work, and increased physician's office visits. The economic burden of this is enormous: in 1992, it was estimated that OM-related Medicaid costs were $555 million for children under the age of 14.[17]

Additionally, OM is linked with hearing loss[37]—while normal conductive hearing levels are under 20 dB,[138] otitis media with effusion is related to a conductive hearing level of 25-30 dB.[21] Due to this hearing loss, there is particular concern that children with chronic or recurrent OM may experience developmental delays. Some studies indicate that longer time spent with OM results poorer reading and verbal abilities and overall lower IQ.[104] Additionally, some studies have associated chronic OM with distinctive structural changes to the middle ear.[21]

2.1.1. ***Otitis media with effusion (OME)***

Otitis media with effusion (OME) is characterized by fluid in the middle ear without any symptoms of acute ear infection (e.g., fever, pain). It is estimated that 90% of children will have at least one episode of OME by age 10.[171] While many episodes of OME resolve spontaneously with no medical intervention, approximately 30 to 40% of OME cases will develop into chronic OME, which is characterized as OME that persists for at least three months.[155,159,175]

OME occurs when fluid collects in the middle ear due to Eustachian tube dysfunction, often in response to respiratory infections, allergies, or other irritants.[123] It most frequently occurs in young children, as their underdeveloped immune system that makes them highly susceptible to respiratory infections which can lead to middle ear inflammation, but their immature Eustachian tube function and anatomy can prevent effective clearance of the middle ear into the nasopharynx. OME is diagnosed via pneumatic otoscopy,[105] which tests the movement of the ear drum; ears with middle ear effusion are often stretched taut and have limited or lack of movement when air is blown into the ear during otoscopy.

OME is often asymptomatic, although those with OME often report a "fullness" in the middle ear—likely due to the accumulated fluid— that can result in conductive hearing loss. OME is associated with an average 28 dB conductive hearing level—approximately 8 dB worse than children with normal hearing.[138] As a result of reduced hearing, there is concern that OME, especially chronic OME, may impact child development with regards to language, behavior, and academic achievement. Additionally, chronic OME has physiologic and anatomic adverse effects, including increased risk for cholesteatoma, characterized as accumulated keratinizing epithelium; retraction pockets and atelectasis, which are weakened portions of the ear drum that have collapsed; acute otitis media (AOM); cysts in the middle ear; and tympanic scarring.[105,138]

At especially high risk for OME are children with craniofacial disorders, Down syndrome, or cleft palate, largely due to inherent anatomic features that reduce Eustachian tube function. One prospective study of 50 children found that 97% children with uncorrected cleft palates will have at least one episode of OME by the age of 2.[41]

2.1.2. *Acute otitis media (AOM)*

Acute otitis media (AOM), more commonly known as an ear infection, is bacterial or viral in nature and frequently presents as sudden onset of inflammation of the middle ear. The most common pathogens of AOM in the United States and the United Kingdom are *Streptococcus pneumonia*, *Haemophilus influenze*, and *Moraxella catarrhalis.*[36] Symptoms include ear pain, irritability, loss of balance, fever, and loss of hearing.[1] It has been shown that 15% to 20% of preschoolers will develop recurrent AOM,[134] which is defined as 3 or more separate episodes of AOM the past 6 months, or at least 4 separate episodes within the past 12 months with at least 1 in the past 6 months.[138]

AOM usually affects about half of children by age 1; by age 3, almost 70% of children will have been diagnosed with an episode of AOM.[133] AOM incidence than tapers off, rarely occurring after the age of 7.[25]

Similar to OME, AOM is exacerbated by Eustachian tube dysfunction. As such, children with AOM also have reduced hearing that may cause developmental delays, in addition to presenting with many of the same quality of life issues. As with OME, children with craniofacial disorders, Down syndrome, or cleft palate are also at increased risk for AOM, as Eustachian tube dysfunction is prevalent in these conditions.

Due to the bacterial or viral etiology of AOM, upper respiratory infection is a risk factor for developing the condition. Other risk factors include exposure to irritants, such as cigarette smoke. Although AOM is distinct from OME, the two conditions exist on a continuum; all children who have AOM are thought to experience some period of OME after the infection clears,[18] and as mentioned previously, chronic OME puts children at risk for AOM.

2.2. Technology: Tympanostomy Tubes

Tympanostomy tube insertion is the primary surgical treatment for otitis media, and is performed in approximately 667,000 children each year.[34] Approximately 1 mm in diameter, functioning tubes equalize middle ear pressure with atmospheric pressure and allow fluid drainage, alleviating symptoms of otitis media.

Ventilation of the middle ear with tympanostomy tube progenitors such as fish bone and cat gut were first documented in the early 18th century,[4] but it was not until the early 1950's that tympanostomy tube insertion as we know it today gained traction.[137]

Description and types of tubes

There are more than 100 FDA-approved tympanostomy tube devices[65] used to help ventilate the middle ears to treat otitis media. Tubes are made of different materials such as plastic, metal, or biocompatible ceramic. Common manufacturers of FDA-approved devices include Exmoor Plastics Ltd., Xomed-Treace Inc., and Treace Medical. Commonly used tubes types in this report include the following:

- Shepard Tubes: Shepard tubes (sometimes "Sheppard") are a grommet-style tube with a flared hourglass shape that extrudes between 6 and 10 months.[51,66] These tubes are made from silicone or fluoroplastic, and are manufactured by Xomed, Inc.[101,166]

- Shah Tubes: Shah Tubes are a grommet-style tube with a single circular beveled flange, with a mean extrusion time of greater than 12 months.[66,87] These tubes are made of fluoroplastic and polyethylene, and are manufactured by Exmoor plastics, Ltd.[101,165]
- Armstrong Tubes: Armstrong tubes are a grommet-style tube with one 90 degree flange and one angled flange. They have a mean extrusion time of 16.5 months.[85] Made from fluoroplastics and polyethylene, these tubes are manufactured by Treace Medical, Inc.[101,163]
- Donaldson Tubes: Donaldson tubes are a grommet-style tube with two equally-sized flanges, and have a mean extrusion time of 11 months.[57] These tubes are made from silicone or fluoroplastic, and are manufactured by Xomed, Concept, Inc., Treace Medical, Inc., and Exmoor Plastics, Ltd.[101,164]
- Bevel Bobbins: Bevel Bobbins are a grommet-style tube with one flared flange, and are similar to a collar button tube. These tubes are made from fluoroplastics and silicone, and are manufactured by Baxter, Reuter, and Circon/Gyrus ACMI.

Tubes are of varying length, diameter, and flange size or angle to accommodate various patient indications, such as age, comorbidities, operator ease, and how long the tubes are intended to remain in place. Tubes intended to last less than 15 months are considered short-term, while those intended to last greater than 15 months are considered long-term.[68] Devices with small flanges, such as a grommet or bobbin, fall out more quickly than devices with large flanges, such as the T-tube, which has one large flange that is not affected by epithelial buildup on the outside of the tympanic membrane.[45] Some tubes are designed to be easier to grip and maneuver for the operator during insertion, such as the Shah Ventilation tube. Mechanistically, tubes fall out due to the accumulation of migration keratin between the tube flange and the surface of the tympanic membrane, which eventually causes the tube to become extruded naturally.

2.2.1. *Procedure*

Tubes are indicated for drainage of chronic otitis media with effusion, or persistent acute otitis media that has failed medical therapy, [138] and can be inserted unilaterally or bilaterally. The procedure takes 10 to 15 minutes to complete.[22] In the pediatric population, tympanostomy tube insertion is conducted using general anesthesia. Surgeons have found no difference in effusion attributable to anesthesia use.[110,151]

After anesthesia has been administered, surgeons will make a myringotomy incision to prepare the tympanic membrane for tube insertion. There are multiple locations on the tympanic membrane used by surgeons for tube insertion, though there is no significant difference in tube retention time between tubes inserted superiorly or anteriorly.[63,170] The pars tensa is the most common insertion site, while the posterosuperior quadrant is rarely used.[68] Surgeons often aspirate fluid persisting in the middle ear prior to tube insertion.

After myringotomy, the tube is inserted to span the tympanic membrane and keep the incision open for the ventilation of the middle ear. Co-interventions such as prophylactic antibiotic drops[108,119,124,128] or corticosteroids[143] can be used at the time of tube insertion to prevent complications such as tube otorrhea, which is discharge from the ear originating from either the external auditory canal, middle ear, mastoid, inner ear, or intracranial cavity.[28] Tube extrusion is dependent on the model of tube used; common extrusion times are discussed above for common tube types in this report. It is recommended that children have check-ups at 4- to 6-month intervals to confirm tube function, evaluate middle ear status, detect any anatomic changes to the middle ear, as well as to reassess efficacy of tubes to manage otitis media.[137]

2.2.2. *Anticipated outcomes*

Tubes have been shown to be effective at managing chronic OME, with systematic reviews indicating that insertions reduce middle ear effusion by 32% in the first year and improve average hearing levels from 5-12 dB.[138] Tube efficacy at managing recurrent AOM is less supported, with many systematic reviews indicating little evidence or small short-term benefits.[138] Overall, tube insertions have been shown to improve quality of life for children and parents.[138] It should be noted that these are all systematic reviews that have been conducted in otherwise healthy children. Tubes have been shown to improving hearing, but these improvements dissipate in the long-term; a systematic review[20] for children receiving grommets with chronic OME showed that hearing benefit is greatest at 3 months, but is reduced at 6 to 9 months.

2.2.3. *Consequences and adverse events*

Adverse events related to tympanostomy tubes can be either transient (e.g., otorrhea) or cosmetic (e.g., cholesteatoma).[135] The most common adverse events and their incidences in children with tubes are described below.

Tympanostomy tube otorrhea

Tympanostomy tube otorrhea is the most common adverse event associated with tube insertion. Otorrhea risk is greater for those with AOM.[137] Otorrhea occurs in 10-20% of children soon after tympanostomy tube insertion, and in approximately 30% of children while tube remains in place. Approximately 4% of children will go on to develop chronic otorrhea.[137] Young age, recurrent AOM as an indication for tube placement, a recent history of recurrent respiratory tract infections, and presence of older siblings were also predictors of otorrhea occurrence.[168]

Cholesteatoma

Cholesteatomas are abnormal skin growths in the middle ear that can grow in size, casing hearing loss, dizziness, or even muscle weakness.[2] Managed early, cholesteatomas are treatable with antibiotics, ear drops, and cleaning of the ear; otherwise, surgery is needed for larger cholesteatomas. Cholesteatoma incidence in tube-extruded ears occurs in approximately 0.7% of children with OM.[71] Cholesteatomas can result from chronic otitis media.

Blockage of Tube Lumen

The tube lumen must be clear in order to function, but blockage by mucus, blood, or other secretions can occur in approximately 7.4% of patients; the risk is higher in long-term tubes such as t-tubes.[97,137] Blockage can be treated by inserting otopical drops for about a week.[137]

Granulation Tissue

Granulation tissue, or granulomas, are accumulated squamous debris that forms around the tube and are estimated to develop in 8% of children.[137] These can be effectively treated with topical corticosteroid and antimicrobial drops, and often resolve after one or two weeks of treatment.[137]

Premature Extrusion

Early extrusion happens when tubes spontaneously fall out within 6 months of the insertion procedure.[27] Tubes may extrude early the tympanic membrane has been weakened by atrophy or atelectasis, or previously treated with tubes. Often this is corrected by reinsertion of tubes, which presents with all the associated harms of anesthesia, perforation, as well as potentially weakening the tympanic membrane, a precursor to other adverse events such as attic retraction and cholesteatoma.

Tympanosclerosis

Tympanosclerosis is characterized by formation of generally asymptomatic plaques of calcium and phosphate crystals that form in response to trauma, such as insertion of tympanostomy tubes.[28]

Incidence ranges from 11-59%.[52] Hearing loss a result of tympanosclerosis has been reported to be less than 0.5 dB.[161]

Persistent Perforation of the Tympanic Membrane

After tubes have been extruded, a perforation in the tympanic membrane may persist. The risk for persistent perforation is greater in long-term tubes (about 9%) than in short term tubes (about 0.5-2%).[137] This can be resolved via surgical closure, although a 6- to 12-month observation period is recommended since most perforations will resolve naturally. Tympanic membrane perforations are seen in approximately 2.2% of children following short-term grommet tubes, and 16.6% of children following long-term t-type tubes.[135]

Atelectasis and Retraction Pockets

Atelectasis is described as general atrophy or membrane collapse that is not a result of prior tube insertion, but rather Eustachian tube dysfunction.[137] Retraction pockets occur when part of the tympanic membrane collapses into the middle ear as a result of a weakened tympanic membrane after tube extrusion.[106,137] Retraction pockets are a preliminary to the formation of a cholesteatoma, as the pocket can begin to collect debris.[137] In a meta-analysis of children with recurrent AOM and chronic OME, incidence of retraction pockets after tube extrusion was shown to be 3.1%.[71]

Harms of Anesthesia

The adverse events of general anesthesia in children undergoing tube insertion is little studied, but is generally considered safe.[64] A retrospective case series review[64] in 3198 children presenting with chronic OM or AOM undergoing bilateral myringotomy and tube insertion indicated an 8.8% incidence of adverse events during and after the tube insertion procedure, with only major events constituting 1.8% of these. Researchers analyzed incidence of events in this group based on the American Society of Anesthesiologists physical class status, and found that children with mild systemic disease were more likely to experience perioperative adverse events.

2.2.4. *Costs*

It is estimated that OM expenditures for the pediatric population in the United States are about $2 billion.[150] There are a variety of costs associated with OM, such as direct costs, which include office visits, medications, and associated procedures; indirect costs, such as parental wages lost for time off work, costs for transportation to and fro the physician's office, or costs of a caregiver; and intangible costs, such as child and parent distress.[148] It is estimated that the cost per episode of AOM ranges from $108 to $1,330; for OME, costs can range from $120 to $406 for medical management, with surgical treatment ranging from $2,173 for tube insertions and $3,334 for tube insertion in conjunction with adenoidectomy.[148]

2.3. Comparator Treatments

Other treatment options for OME or AOM include antibiotics or other medications such as steroids or mucolytics, myringotomy (eardrum incision), adenoidectomy, or autoinflation of the Eustachian tube. In addition, because otitis media often resolves spontaneously, especially within the first six months, and may not cause long-term hearing or developmental problems, watchful waiting or delayed tube placement may be considered.

2.3.1. *Watchful waiting or delayed tube insertion*

Watchful waiting (WW) describes a treatment approach in which no surgical treatment is applied, but children are actively reassessed to determine if there is a change in health status and if more active

treatment should be implemented due to changes in symptomatology. It is a common tactic for treating chronic OME and recurrent AOM, as both often resolve without further treatment; one study in over 800 children indicated that 52% of OME cases resolve within 4 months of diagnosis.[175]

2.3.2. *Myringotomy*

Myringotomy is indicated to relieve severe otalgia and to drain the middle ear of fluid;[135] it is performed by creating an incision in the middle ear to allow for relief of pressure and drainage of effusion. The incision can be created by either a cold knife or a laser; cold knife myringotomy allows for ventilation for approximately 72 hours, and laser myringotomy allows for ventilation for anywhere from 1 to 7 weeks.[32,40,76,79,89,126,153,176] Along with insertion of tympanostomy tubes, it is the most common pediatric surgical procedure that requires general anesthesia, and as such comes with all the associated complications.[15] It has been shown that contact diode laser myringotomy takes half as long to perform compared to tympanostomy tube insertion and has a similar complication incidence rate, but that overall, ventilation times were half that of tympanostomy tube insertion.[35]

2.3.3. *Adenoidectomy*

Adenoidectomy is indicated for those who have obstructive sleep apnea, as well as those who have frequent throat infections that cause enlargement of the adenoids, which subsequently block Eustachian tubes, causing recurrent AOM or chronic OME.[145] Although adenoidectomy is not guideline-recommended for children presenting without adenoid disease,[15] studies have found that it is effective for treating OM in this population.[49,113] Adenoidectomy is often performed in conjunction with a tonsillectomy (i.e., adenotonsillectomy). Performed under general anesthesia, it presents with the usual risks associated with an anesthetic procedure. Current reports of adenoidectomy effectiveness are mixed; one SR indicated that tympanostomy tubes were more effective than adenoidectomy at reducing frequency of otitis media, reducing time with otitis media, but is effective at reducing otitis media recurrence.[30] When adenoidectomy is performed in conjunction with tube insertion or a myringotomy, it has been effective in medically non-responsive cases of OM.[15]

2.3.4. *Antibiotics*

Antibiotics are used to treat cases of recurrent AOM, due to its bacterial etiology. Antibiotic treatment can be administered systemically or topically. When administered topically, antibiotics are usually delivered to the ear by a dropper. However, current guidelines discourage prescription of prophylactic antibiotics for recurrent AOM,[82] and in general, most advise judicious use of antibiotics due to rising antibiotic resistance.[129] Ofloxacin is the only FDA-approved topical antimicrobial for treating otorrhea in a perforated tympanic membrane. Other topical antibiotics include amoxicillin-clavulanate and ciprofloxacin ophthalmic solution.

2.3.5. *Other medications*

Medical therapy in the form of mucolytics, steroids, and analgesics are often indicated to help alleviate respiratory infection, middle ear inflammation, and otalgia associated with AOM and OME. However, analgesics and topical anesthetics have been shown to reduce earache,[36] but mucolytics and antihistamines with oral decongestants have poor evidence to support their utility for relieving OME in children.[174] Additionally, steroid therapy has been shown to not significantly resolve OME.[132]

2.3.6. *Autoinflation of the Eustachian tube*

Autoinflation describes the process of forcing air into the Eustachian tube, middle ear, and mastoid cavities to normalize inner ear pressure, thus relieving pressure resulting from middle ear effusion.[15]

Due to the somewhat complicated nature of the maneuver for children, it is very unlikely that effusion can be completely cleared via autoinflation, and as such, is not recommended for alleviating symptoms of AOM or OME.[15] However, because of low costs, it is a viable adjunct to watchful waiting for natural resolution of OM.[121]

2.3.7. *Complementary and alternative medicine treatments*

Complementary and alternative medicine (CAM) treatments include homeopathy, chiropractic administration, xylitol, elimination diets for food allergies, herbal medicines (e.g., Echinacea), naturopathic ear drops, and acupuncture.[69] No studies were identified that evaluated the use of CAM treatments on children with chronic OME or recurrent AOM.

2.4. Clinical Guidelines

The National Guideline Clearinghouse (NGC), major bibliographic databases, professional societies, and Medline were searched for guidelines related to insertion of tympanostomy tubes in children presenting with otitis media with effusion (OME) or acute otitis media (AOM). Key word searches were performed: ("otitis media" OR "otitis media with effusion" OR "acute otitis media" OR "ear infection") AND ("tympanostomy" OR "ventilation" OR "pressure equal*").

Guidelines from the following sources are summarized:

- American Academy of Otolaryngology-Head and Neck Surgery Foundation
- The Darwin Otitis Guidelines Group in collaboration with the Office for Aboriginal and Torres Strait Islander Health Otitis Media Technical Advisory Group
- British Columbia Medical Association, British Columbia Ministry of Health Services, Guidelines and Protocols Advisory Committee
- National Institute for Health and Care Excellence (NICE)
- Korean Society of Otology
- Tsilis et al. 2013[162]
- American Academy of Pediatrics

Details of each included recommendation for insertion of tympanostomy tubes in children with OME or AOM, including the class/grade of recommendation and level of evidence, can be found in Table 2.

A summary of the guidelines from the more prominent organizations in which the level of recommendations were evaluated is provided below.

OME

American Academy of Otolaryngology-Head and Neck Surgery Foundation, 2013: *Clinical Practice Guideline: Tympanostomy Tubes in Children:* It is recommended that clinicians provide tympanostomy tube insertion in: children with chronic bilateral OME and documented hearing difficulties or symptoms attributable to OME (e.g., reduced quality of life); children with chronic unilateral OME and symptoms attributable to OME (e.g., reduced quality of life); and children at risk for developmental disorders (e.g., cleft palate) with unilateral or bilateral OME that is unlikely to resolve quickly.

AOM

American Academy of Pediatrics, 2013: *Clinical Practice Guideline: The Diagnosis and Management of Acute Otitis Media.* Tubes are recommended for children with recurrent AOM.

American Academy of Otolaryngology-Head and Neck Surgery Foundation, 2013*: Clinical Practice Guideline: Tympanostomy Tubes in Children:* Tubes are recommended only when unilateral or bilateral middle ear effusion is present at the time of assessment, and if clinicians have determined a child is at risk for developmental problems.

Table 2. Clinical Guidelines

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
OME						
The American Academy of Otolaryngology-Head and Neck Surgery Foundation[138] *Clinical Practice Guideline: Tympanostomy Tubes in Children (2013)*	2005 through February 2012	Children 6 months to 12 years of age, with tympanostomy tubes or being considered for TT in any case setting, as an intervention of OM of any time.	Tympanostomy tube insertion, including indications for tube placement, preoperative care, and postoperative care	4 guidelines, 15 systematic reviews or meta-analyses	1. Clinicians should not perform tympanostomy tube insertion in children with a single episode of OME of less than 3 months' duration. (Recommendation (against)*) 2. Clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer (chronic OME) OR prior to surgery when a child becomes a candidate for tympanostomy tube insertion. (Recommendation*) 3. Clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer (chronic OME) AND documented hearing difficulties. (Recommendation*) 4. Clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) AND symptoms that are likely attributable to OME that include, but are not limited to, vestibular problems, poor school performance, behavioral	Grade C† Grade C† Grade B† Grade C†

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					problems, ear discomfort, or reduced quality of life. (Option*)	
					5. Clinicians should reevaluate, at 3- to 6 month intervals, children with chronic OME who did not receive tympanostomy tubes, until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected. (Recommendation*)	Grade C†
					6. Clinicians should determine if a child with… OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors. (Recommendation*)	Grade C†
					7. Clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME). (Option*)	Grade C†
					8. In the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding	Grade C†

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					the expected duration of tube function, recommended follow-up schedule, and detection of complications. (Recommendation*) 9. Clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics for children with uncomplicated acute TT otorrhea. (Strong Recommendation*) 10. Water precautions: Clinicians should not encourage routine, prophylactic water precautions (use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes. (Recommendation (against) *)	Grade B† Grade B†
The Darwin Otitis Guidelines Group in collaboration with the Office for Aboriginal and Torres Strait Islander Health Otitis Media Technical Advisory Group[37] *Recommendations for clinical care guidelines on the management of otitis media in Aboriginal and Torres Strait Islander populations (2010)*	2001 – April 1, 2010	Children (specifically in the Aboriginal and Torres Strait Islander populations)	Tympanostomy tubes	8 SRs, 1 guideline	**Management of Persistent Otitis Media with Effusion (OME):** 1. Refer the child (who is not at high risk for chronic suppurative OM) for grommet insertion if: • the child has a persistent hearing loss >20dB, • the parents understand that the operation will provide a modest, • improvement in hearing for 6-9 months, and • surgery is consistent with the parents' preferences.	Grade A‡

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					The likelihood of benefit from grommets increases with greater levels of hearing loss.	
				1 non-systematic review 3 SRs, 3 clinical guidelines 1 clinical guideline	2. Refer the child (who is not at high risk for chronic suppurative OM) for grommet insertion if: • the child has a persistent hearing loss >20dB, • the parents understand that the operation will provide a modest, • improvement in hearing for 6-9 months, and • surgery is consistent with the parents' preferences. The likelihood of benefit from grommets increases. 3. Consider referral for adenoidectomy if bilateral OME has occurred despite previous grommet (tympanostomy tube) insertion or if the child is at high risk of chronic suppurative OM. 4. Grommets plus adenoidectomy can be an option for children >3 years who have recurrent persistent OME and hearing loss after previous grommet insertion, severe nasal obstruction, or chronic adenoiditis.	Good practice point (GPP)‡ Grade B‡ Grade B‡
British Columbia Medical Association,	NR	Otherwise healthy children over the age of 6 months	Tympanostomy tubes	NR	• If a child with OME does become a candidate for surgery,	NR

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
British Columbia Ministry of Health Services, Guidelines and Protocols Advisory Committee[102] *Otitis Media: Acute Otitis Media (AOM) and Otitis Media with Effusions (OME) (2010)*		presenting with AOM or OME. Does not include children with craniofacial abnormalities, immune deficiencies, and complications of AOM (e.g. mastoiditis, facial paralysis, etc.) or serious underlying disease.			tympanostomy tube insertion is the preferred initial procedure. • Surgical treatment of OME may prevent middle ear complications, including: atelectatic tympanic membrane, permanent conductive hearing loss, cholesteatoma, etc.	
National Institute for Health and Care Excellence (NICE)[107] *Surgical management of otitis media with effusion in children, NICE clinical guideline 60 (2008)*	NR	Children under the age of 12 years presenting with OME. Special populations: Children with cleft palate, Down's syndrome	Tympanostomy tubes	NR	**Appropriate time for intervention:** • The persistence of bilateral OME and hearing loss should be confirmed over a period of 3 months before intervention is considered. The child's hearing should be re-tested at the end of this time. • During the active observation period, advice on educational and behavioral strategies to minimize the effects of the hearing loss should be offered. **Children who will benefit from surgical intervention:** • Children with persistent bilateral OME documented over a period of 3 months with a hearing level in the better ear of 25–30 dB HL or worse averaged at 0.5, 1, 2 and 4 kHz (or equivalent dBA where dB HL not available) should be considered for surgical intervention.	NR

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					• Exceptionally, healthcare professionals should consider surgical intervention in children with persistent bilateral OME with a hearing loss less than 25–30 dB HL where the impact of the hearing loss on a child's developmental, social or educational status is judged to be significant. **Surgical interventions:** • Once a decision has been taken to offer surgical intervention for OME in children, the insertion of ventilation tubes is recommended. Adjuvant adenoidectomy is not recommended in the absence of persistent and/or frequent upper respiratory tract symptoms. • Children who have undergone insertion of ventilation tubes for OME should be followed up and their hearing should be re-assessed. **Management of OME in children with Down's syndrome** • The care of children with Down's syndrome who are suspected of having OME should be undertaken by a multidisciplinary team with expertise in assessing and treating these children.	

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					• Hearing aids should normally be offered to children with Down's syndrome and OME with hearing loss. • Before ventilation tubes are offered as an alternative to hearing aids for treating OME in children with Down's syndrome, the following factors should be considered: • the severity of hearing loss • the age of the child • the practicality of ventilation tube insertion • the risks associated with ventilation tubes • the likelihood of early extrusion of ventilation tubes **Management of OME in children with cleft palate:** • The care of children with cleft palate who are suspected of having OME should be undertaken by the local otological and audiological services with expertise in assessing and treating these children in liaison with the regional multidisciplinary cleft lip and palate team. • Insertion of ventilation tubes at primary closure of the cleft palate should be performed only after	

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					careful otological and audiological assessment. • Insertion of ventilation tubes should be offered as an alternative to hearing aids in children with cleft palate who have OME and persistent hearing loss.	
Korean Society of Otology[80] *Korean Clinical Practice Guidelines: Otitis Media In Children (2012)*	2004 - 2009	Otherwise healthy Korean children under 15 years old presenting with OME.	Tympanostomy Tubes	1 systematic review, 5 studies (study type NR)	• Ventilation tube insertion is the preferred initial procedure when a child becomes a surgical candidate. (Recommendation§) • Surgical intervention is necessary when a child shows hearing loss of a moderate degree or worse, and when the tympanic membrane is anticipated to develop irreversible changes. • When OME persists over the 3-month observation but the hearing threshold in the better ear is lower than the criterion demanding surgical intervention, the duration of disease is considered as the most crucial factor to determine whether surgical intervention should be performed.	Grade B§
Tsilis 2013[162] *Chronic Otitis Media in Children: An Evidence-Based Guide for Diagnosis and*	NR	Children presenting with chronic OM.	Tympanostomy Tubes	NR	• For those presenting with chronic otitis media and a retracted tympanic membrane, tympanostomy tube placement and regular follow-up should be	NR

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
Management (2013)					attempted when the fundus of the retraction pocket is visible and clean.	
AOM						
American Academy of Pediatrics[82] *Clinical Practice Guideline: The Diagnosis and Management of Acute Otitis Media (2013)*	NR - October 2011	Otherwise healthy children without underlying conditions that may alter the natural course of AOM, aged 6 months to 12 years or age.	Tympanostomy Tubes	3 RCTs, 1 SR, 1 multicenter nonrandomized observational study	• Clinicians may offer tympanostomy tubes for recurrent AOM (3 episodes in 6 months or 4 episodes in 1 year, with 1 episode in the preceding 6 months). *(Option**)* • Benefits: Decreased frequency of AOM. Ability to treat AOM with topical antibiotic therapy. • Risks, harms, cost: Risks of anesthesia or surgery. Cost. Scarring of TM, chronic perforation, cholesteatoma, otorrhea. • Benefits-harms assessment: Equilibrium of benefit and harm. • Value judgments: None • Intentional vagueness: Option based on limited evidence. • Role of patient preferences: Joint decision of parent and clinician. • Exclusions: Any contraindication to anesthesia and surgery.	Grade B†
The American Academy of Otolaryngology-Head and Neck Surgery Foundation[138]	2005 through February 2012	Children 6 months to 12 years of age, with tympanostomy tubes or being considered for TT in any case setting, as an	Tympanostomy tube insertion, including indications for tube placement,	4 guidelines, 15 systematic reviews or meta-analyses	• Clinicians should not perform tympanostomy tube insertion in children with recurrent AOM who do not have middle ear effusion in either ear at the time of	Grade A†

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
Clinical Practice Guideline: Tympanostomy Tubes in Children (2013)		intervention of OM of any time.	preoperative care, and postoperative care		assessment for tube candidacy. (Recommendation (against) *) • Clinicians should offer bilateral tympanostomy tube insertion to children with recurrent AOM who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy. (Recommendation*) • Clinicians should determine if a child with recurrent AOM… is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors. (Recommendation*) • In the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up complications. (Recommendation*) • Clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics for children with uncomplicated acute TTO. (Strong Recommendation*) • Water precautions: Clinicians should not encourage routine, prophylactic water precautions	Grade B† Grade C† Grade C† Grade B† Grade B†

Organization(s) Title (year)	Search Dates	Population Investigated	Intervention	Evidence Base Available	Recommendations	Level of Evidence
					(use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes. (Recommendation (against)*)	
The Darwin Otitis Guidelines Group in collaboration with the Office for Aboriginal and Torres Strait Islander Health Otitis Media Technical Advisory Group[37] *Recommendations for clinical care guidelines on the management of otitis media in Aboriginal and Torres Strait Islander populations (2010)*	2001 – April 1, 2010	Children (specifically in the Aboriginal and Torres Strait Islander populations)	Tympanostomy tubes	4 SRs, 3 clinical guidelines	**Management of recurrent AOM (rAOM)** (defined as 3 episodes of AOM within a 6 months period or 4 episodes within 12 months): Refer for consideration of grommet surgery if: • The child is at low risk of developing chronic suppurative OM, and • rAOM fails to improve on antibiotic prophylaxis (>3 episodes in 6 months or >4 episodes in 1 year).	Grade B‡
Kitamura 2014[75] *Clinical Practice Guidelines for the Diagnosis and Management of AOM in Children in Japan—2013 update (2014)*	2006 - 2009	AOM patients aged <15 years who were free from AOM or OME within one month prior to onset, who do not have a TT inserted, who have no craniofacial abnormality, and who do not suffer from immunodeficiency.	Tympanostomy Tubes	NR	• Insertion of a tympanostomy tube for one year and short-term insertion for one month significantly reduce the frequency of occurrence of recurring otitis media (ROM) (defined as three or more occurrences of AOM within the previous six months, or four or more within the previous 12 months).	NR

AOM: Acute Otitis Media; dBA: A-weighted decibel; HL: hearing level; OM: Otitis Media; OME: Otitis Media with Effusion; TT: Tympanostomy Tube

* Guideline definitions for Evidence-Based Statements:

Strong recommendation: Benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B). In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

Recommendation: The benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation) but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, recommendations may be made based on lesser evidence when high quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. Clinicians should also generally follow a recommendation but should remain alert to new information and be sensitive to patient preferences.

Option: The quality of evidence that exists is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach versus another. Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

No recommendation: No recommendation means there is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms. Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

† Levels for grades of evidence is based on the American Academy of Pediatrics classification scheme, updated for consistency with the Center for Evidence Based Medicine (CEBM) Levels of Evidence.

Grade A: For Treatment and Harm, a Grade A indicates well-designed randomized controlled trials performed on a population similar to the guideline's targetpopulation. For Diagnosis, Grade A indicates a systematic review of cross-sectional studies with consistently applied reference standard and blinding.

Grade B: For Treatment and Harm, Grade B indicates randomized controlled trials and overwhelmingly consistent evidence from observational studies. For Diagnosis, Grade B indicates individual cross-sectional studies with consistently applied reference standard and blinding.

Grade C: For Treatment and Harm, Grade C indicates observational studies such as case control and cohort design). For Diagnosis, Grade C indicates nonconsecutive studies, case-control studies, or studies with poor, non-independent, or inconsistently applied reference standards.

Grade D: Indicates mechanism-based reasoning or case reports.

Grade X: Indicates exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit over harm.

‡ OATSIH NHMRC Grading of Recommendations

A: Body of evidence can be trusted to guide practice.

B: Body of evidence can be trusted to guide practice in most situations.

C: Body of evidence provides some support for recommendation but care should be taken in its application.

D: Body of evidence is weak and recommendation must be applied with caution. GPP (Good Practice Point): No reliable evidence exists directly addressing the impact of recommendation. The recommendation (a Good Practice Point) reflects the consensus view of the multidisciplinary guidelines group and is based on clinical experience.

§ KOREAN OTOLARYNGOLOGY GUIDELINES RECCOMENDATION LEVELS

A: Strong recommendation: The benefits of the recommended intervention clearly exceed the harm, and the quality of evidence is excellent. Implication: Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

B: Recommendation: The benefits of the recommended intervention exceed the harm, but the quality of evidence is not as strong. Implication: Clinicians would be prudent to follow a recommendation, but should remain alert to new information and sensitive to patient preferences.

C: Option: The quality of evidence that exists is suspicious, or well-done studies show little clear advantage. Implication: Clinicians should consider the option in their decision-making, and patient preference may play a substantial role.

D: No recommendation: As pertinent published evidence is lacking, the anticipated balance of benefits and harm is unclear. Implication: Clinicians should be alert to new published evidence that clarifies the balance of benefit vs. harm.

** Guideline definitions for Evidence-Based Statements.

Strong Recommendation: The anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

Recommendation: The anticipated benefits exceed the harms, but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high quality evidence is impossible to obtain but the anticipated benefits outweigh the harms. Clinicians would be prudent to follow a recommendation but should remain alert to new information and sensitive to patient preferences.

Option: Courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to 1 approach over another. Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.

No Recommendation: There is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear. Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

2.5. Previous Systematic Reviews/Technology Assessments

A total of six Health Technology Assessments (HTAs) and 9 high-quality systematic reviews (SRs) provided data on tympanostomy tube insertion in children. These reports are summarized in Table 3 (HTAs) and Table 4 (SRs). The following provides a summary of outcomes from HTAs in which the strength of evidence for each conclusion was evaluated.

Hearing:

- TT versus WW: The 2013 AHRQ report (Berkman 2013[10]) concluded that TT improved hearing up to 9 months (high strength of evidence but had no benefit by 12 to 18 months (low strength of evidence).
- TT versus WW or myringotomy: The 2013 AHRQ report (Berkman 2013[10]) concluded that TT improved hearing at 4 to 6 months (high strength of evidence), but that there was no difference in hearing at 7 to 12 months (low strength of evidence).
- TT + adenoidectomy vs. myringotomy + adenoidectomy TT + adenoidectomy vs. myringotomy + adenoidectomy: The 2013 AHRQ report (Berkman2013[10]) found no difference in hearing at 6 and 12 months and at more than 3 years (low strength of evidence)

Otorrhea:

- TT vs. WW or myringotomy: The 2013 AHRQ report (Berkman 2013) concluded that TT increased otorrhea (moderate strength of evidence).

Attention and Behavioral Outcomes:

- TT vs WW: The 2013 AHRQ report (Berkman 2013) found mixed results in behavior at 6 and 9 months (insufficient strength of evidence) and no difference in behavior at 1 year or more (low strength of evidence).

Academic Achievement:

- TT vs WW: The 2013 AHRQ report (Berkman 2013) found no difference in academic achievement at 6 and 9 months (insufficient strength of evidence) and no difference in behavior at 1 year or more (low strength of evidence.
- TT vs WW or delayed TT: The 2013 AHRQ report (Berkman 2013) showed no difference in cognitive development or academic achievement at age 3, 6, 8 years (low strength of evidence).

Speech and Language Development:

- TT vs WW: The 2013 AHRQ report (Berkman 2013) reported no difference in speech/language at 6, 9, 12 months or more (moderate strength of evidence), nor at 1 year or more (low strength of evidence).
- TT vs WW or delayed TT: The 2013 AHRQ report (Berkman 2013) found no difference in language comprehension or language expression at 6 and 9 months post intervention, nor at ages 3, 6, and 8 (moderate strength of evidence).

Patient Quality of Life:

- TT vs WW: The 2013 AHRQ report (Berkman 2013) found no difference in quality of life at 6, 9, 12 months or more (insufficient strength of evidence).

Auditory processing, Parent Satisfaction with treatment/outcomes, surgery:

- No HTAs reported on this outcome.

AOM:

Hearing:

- TT versus WW or myringotomy: The 2008 SBU report (Hellstrom 2008) reported that TT improved hearing for at least 3 months (strong evidence), but that for children with Downs syndrome, there were fewer children who improved after receiving TT compared to those without TT (limited evidence)

Patient Quality of Life:

- TT versus WW: The 2008 SBU report (Hellstrom 2008) reported that TT improved quality of life in children with long-term secretory OM from 6 weeks to 9 months (moderate evidence).

Otorrhea, Patient Satisfaction with treatment/outcomes, Surgery:

No HTAs reported on these outcomes.

Table 3. Previous Health Technology Assessments

Hta (Year)	Treatment	Critical Appraisal	Conclusion (Evidence Base)	Strength Of Evidence
OME				
Berkman (2013)[10] AHRQ Search dates: Through 8/13/2012	Intervention: • Tympanostomy tubes (TT) Comparator: • Watchful waiting (WW) • Myringotomy • Adenoidectomy • Autoinflation • Steroids (oral or nasal) • Complementary and alternative medicine (CAM) • Tympanostomy tubes (different sizes, shapes, materials and routes or techniques for insertion)	Cochrane risk of bias tool, AMSTAR	TT vs. WW • TT improved hearing up to 9 mos. (MA of 3 RCTs; 1 RCT) (3–6 months: 8.8 dB; 6–9 months: 4.2 dB) • No difference in hearing at 12 or 18 mos. (MA of 4 RCTs) • 32% less time with TT at 1 year or more after surgery (MA or 3 RCTs) • No difference in speech/ language at 6, 9 mos. (MA of 3 RCTs, 1 study)/or at 1 year or more (1 study) • No difference in speech/ language at 1 year or more (1 study) • No difference in cognitive development at 6, 9 mos. (1 study) • No difference in cognitive development at 1 year or more (2 studies) • No difference in academic achievement at 6, 9 mos. (no studies) • No difference in academic achievement at 1 year or more (2 studies) • Mixed results in behavior at 6, 9 mos. (2 studies) • No difference in behavior at 1 year or more (3 studies) • No difference in quality of life at 6, 9 mos. (1 study) • No difference in quality of life at 1 year or more (1 study)	**High** (benefit) **Low** (no difference) **High** (benefit) **Moderate** (no difference) **Low** (no difference) **Low** (no difference) **Low** (no difference) **Insufficient** **Low** (no difference) **Insufficient** **Low** (no difference) **Insufficient** **Insufficient**

Hta (Year)	Treatment	Critical Appraisal	Conclusion (Evidence Base)	Strength Of Evidence
			• TT vs. WW or delayed TT	**High** (benefit)
			• TT decreased persistent OME at 1 year or more (MA of 3 RCTs)	
			• No difference in language comprehension, or language expression at 6, 9 months after intervention or at preschool and elementary school age (ages 3, 6 and 8) (MA of 3 RCTs, and 2 RCTs)	**Moderate** (no difference)
			• No difference in cognitive development at 9 months post-intervention or at preschool or elementary school age (ages 3, 6 and 8) (2 RCTs)	**Low** (no difference)
			• No difference in cognitive development or academic achievement at preschool or elementary school age (ages 3, 6 and 8) (2 RCTs)	**Low** (no difference)
			TT vs. myringotomy	
			• TT reduces time with OME by 42% through 1 year or more (2 cohort studies)	**Moderate** (benefit)
			• No difference? in speech/Language, cognitive development, academic achievement, behavior, Quality of Life (0 studies)	**Insufficient**
			TT vs. WW or myringotomy	
			• TT decreased persistent OME by 13% through 2 years after surgery (MA of 3 RCTs)	**Moderate** (benefit)
			• TT improved hearing by 10 dB at 4 to 6 mos. (MA of 3 RCTs; 1 RCT)	**High** (benefit)
			• No difference in hearing at 7-12 months (MA of 3 RCTs)	**Low** (no difference)
			• TT increased tympanosclerosis incidence (5 studies)	**Moderate** (harms of TT)
			• TT increased otorrhea (4 studies)	**Moderate** (harms of TT)

Hta (Year)	Treatment	Critical Appraisal	Conclusion (Evidence Base)	Strength Of Evidence
			TT + adenoidectomy vs. myringotomy + adenoidectomy • No difference in hearing at 6, 12 mos., and more than 3 years (5 RCTs, 1 nonrandomized) • TT increased tympanosclerosis incidence (3 studies) TT + adenoidectomy vs. WW • TT + adenoidectomy improved hearing for 3 to 24 months (1 study) Comparisons of TTs 14 studies • Length of tube retention was higher in the long term TT (7 RCTs, 3 non-randomized studies) • Longer-term TT increased otorrhea (9 studies) • Hearing TT vs. CAM • No evidence	**Low** (no difference) **Moderate** (harms of TT) **Low** (benefit) **Insufficient** **Low** (harms of longer-term TT) **NR** (no evidence) **NR** (no evidence)
Ndegwa (2014)[109] CADTH Search dates: 1/1/09 – 7/7/14 (updated until 8/25/14)	Intervention: • TULA Iontophoresis system and Tube Delivery System Comparator: • NR	NR	**Adverse events (3 prospective open label single group assignment clinical studies, 1 has been published)** • No serious adverse effects relating to the TULA Tube Delivery System were reported • No safety issues or complications associated with the Tula Iontophoresis system or the local anesthetic mixture were noted	**NR**
Health Information and Quality	Intervention: • Grommet insertion with myringotomy	NR	**Grommet insertion vs. WW** • Grommet insertion has small effects on hearing outcomes, with all effects diminished after 6-9 months,	**SoE NR** (1 review, n = 1728 children)

Hta (Year)	Treatment	Critical Appraisal	Conclusion (Evidence Base)	Strength Of Evidence
Authority (2013)[61] Ireland Search dates: Search done in January 2013 (search dates otherwise unspecified)	Comparator: • WW		by which time natural resolution leads to improved hearing • Mean hearing level was 12 dB better (95% CI 10 to 14 dB) at 3 months grommet insertion (1 RCT) • Mean hearing level was 4 dB better (95% CI 2 to 6 dB) at 6-9 months with grommet insertion (3 high quality nonrandomized trials) • No difference in mean hearing levels at 12-18 months (3 high quality non randomized trials) No effect was found on language or speech development or for behavior, cognitive or quality of life outcomes **Adenoidectomy + unilateral TT vs. WW** A beneficial effect on the resolution of OME RD 22% (95% CI 12% to 32%) and 29% (95% CI 19% to 39%) at 6 and 12 months compared to controls (3 trials) **Cost-effectiveness of grommet insertion** • Insertion of grommets is a cost-effective treatment for persistent or bilateral OME Cost for grommet insertion was estimated at £1,208 based on the National Tariff 2006/7 (England) Cost/case of surgery in Ireland for myringotomy + tube insertion is €3,109 (inpatient) or €868 (outpatient) • Mean costs per child during one year of follow-up were $454 in the grommet group and $120 in the watchful waiting group On average, an additional investment of $334 per patient was needed for grommet insertion (societal perspective).	**SoE NR** (1 review, n = 2712 children) **SoE NR** (Economic model from the NICE guideline) **SoE NR** (Ireland: Health Service Executive report) **SoE NR** (Economic evaluation in The Netherlands)
AOM				
Shekelle (2010)[149]	Intervention: Tympanostomy tubes	RCTs: Jadad, Moore, Carroll et	Regarding the prevention of AOM in children with ROM, the available evidence from prior SRs shows that TT placement	**SoE NR** (2 studies)

Hta (Year)	Treatment	Critical Appraisal	Conclusion (Evidence Base)	Strength Of Evidence
AHRQ Search dates: January 1998 – July 2010	(TT) Comparator*: • TT + adenoidectomy • WW	al. (1996) criteria Cohorts and case-controls: McMaster University Group criteria Diagnostic evaluations: QUADAS criteria SRs: AMSTAR criteria	plays a significant role in maintaining a disease-free state in the first 6 months after tube insertion	
Hellström (2008)[62] SBU From summary report, full text in Swedish Search dates: 1966 – April 2007	Intervention: Tympanostomy tubes (TT) Comparator: • Watchful waiting (WW) • Myringotomy • Adenoidectomy • Antibiotics • Tympanostomy tubes (different materials)	Graded using SBU's standard templates for assessment (each conclusion given evidence grade between 1 (strong scientific evidence) and 3 (limited scientific evidence))	• TT vs. WW or myringotomy • TT decreased recurrence of AOM by more than half from 6 mos. to 1 year (2 studies) • No difference in AOM recurrence at 1 or 2 years (1 study) • Improved hearing for at least 9 mos. (3 studies) • Fewer children with Down's syndrome had better hearing after TT than children without it (2 studies) **TT vs. WW** • TT improves quality of life in children with long-term secretory OM for 6 weeks to 9 mos. **TT vs. Pharmacological options** • Amoxicillin was significantly more effective at long term prevention of OM (1 study) **Titanium TT vs. plastic TT** • No difference in period of functionality or the risk of infection between titanium and plastic TT (1 study)	**Moderate** (favoring TT) **Limited** (no difference) **Strong** (favoring TT) **Limited** (favoring WW or myringotomy) **Moderate** (favoring TT) **Insufficient** **Insufficient**

Hta (Year)	Treatment	Critical Appraisal	Conclusion (Evidence Base)	Strength Of Evidence
			Removing TT that do not come out spontaneously vs. leaving them • No benefit identified • TT complications • Chronic perforations appear in up to 5% of ears with TT and in 1% of ears with OM without TT • Myringosclerosis appears in approximately half of ears with TT and 1-20% of ears with OM without TT • TT otorrhea unrelated to the procedure is common (26-83%) **Cost effectiveness of TT for acute or secretory OM** (2 studies; authors performed a health economic model analysis) • Evidence is insufficient to determine cost-effectiveness for recurrent acute OM or long-term secretory OM	**NR** **Limited** **Moderate** (favoring no TT insertion) **NR** **Insufficient**
Mixed Population (OME or AOM)				
Boonacker (2014)[18] NHS Search dates: Through June 7, 2012	Intervention: • Adenoidectomy alone or with myringotomy • Adenoidectomy with unilateral or bilateral grommet Comparator: • Unilateral or bilateral grommets • Non-surgical treatment or myringotomy	The Cochrane Collaboration tool	**Adenoidectomy vs. non-surgical vs. grommets** (10 RCTs) • 56% of patients treated non-surgically failed to improve at 12 months† • 32% of patients with adenoidectomy alone failed to improve at 12 months • 45% of patients with non-surgical treatment or grommets alone failed to improve at 12 months	**SoE NR** (8 RCTs at Low risk of bias) **SoE NR** (2 RCTs at Moderate risk of bias)

AHRQ: Agency for Healthcare Research and Quality; AOM: Acute otitis media; CADTH: Canadian Agency for Drugs and Technologies in Health; CAM: complementary and alternative medicine; CI: confidence interval; HIQA: Health Information and Quality Authority; MA: meta-analysis; MCID: minimum

clinically important difference; NHS: National Institute for Health Research; NICE: National Institute for Health and Care Excellence; NR: not reported; OME: otitis media with effusion; RCT: randomized controlled trial; RD: risk difference; SBU: Swedish Council on Health Technology Assessments in Health Care; SoE: strength of evidence; TT: tympanostomy tubes; WW: watchful waiting

*Also included KQs involving diagnosis of AOM and effects of vaccination.

†Treatment failure was defined as a composite outcome consisting of no improvement in number of OM episodes per person month, no improvement in prevalence of OME at FU visits, no improvement in mean hearing level at FU visits, crossing over from watchful waiting to surgical treatment arm, or additional surgery.

Table 4. Previous Systematic Reviews

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
OME					
Kuo (2014)[4]	Through November 2013	Children ≤ 18 years old Special population: Cleft palate (including unilateral or bilateral cleft palate with or without cleft lip, cleft palate only, and sub mucous cleft palate)	GRADE and Oxford Centre for Evidence-Based Medicine Levels of Evidence	**TT vs No TT*** Evidence base: 1 prospective cohort study and 8 retrospective cohort studies; N = 702 Outcomes: Speech Language Complications and sequelae	***Efficacy:*** **TT vs No TT** • Tympanostomy tube insertion may improve hearing outcomes in children with cleft palate compared with those who undergo conservative treatment, with improvements remaining for 1 – 9 years after surgery. • Tympanostomy tube insertion may benefit children with cleft palate and OME in the development of speech and language. ***Safety:*** **TT vs No TT** • Children who have undergone tympanostomy face a higher risk of complications than those who have not undergone tympanostomy, with the most common complications being eardrum retraction and tympanosclerosis.

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
Browning (2010)[20] (Cochrane)	Latest search completed March 22, 2010	Children 1-12 years old	Cochrane Risk of Bias Tool	**TT vs. Non-surgical treatment** Evidence base: Total: 10 RCTs; N = 1728 By-child analysis: 3 RCTs; N = 523 By-ear analysis: 3 RCTs; N = 230 ears Outcomes: Hearing level Time with effusion Language and speech development Cognitive development Behavior Quality of Life Repeat/revision surgery Adverse effects	***Efficacy:*** **TT vs. Non-surgical treatment** • On a by-child analysis, grommets are mainly beneficial in the first six months; at twelve months follow up, there are no differences in mean hearing levels due to natural resolution. • On a by-ear analysis, grommets maintain a hearing benefit in the second year. • There is a small but significant beneficial effect for time with effusion in children treated with tympanostomy tubes. • TT had no effect on language/speech development, behavior, cognitive, or QoL outcomes compared to watchful waiting/active monitoring. • About 30% of children that have TTs have re-operations, but that rate has been shown to be reduced to about 10% if adjuvant adenoidectomy is performed at the same time as TT insertion. ***Safety:*** **TT vs. Non-surgical treatment** • Tympanosclerosis was seen in about a third of ears that received grommets.
Williamson (2007)[9] (BMJ Clinical Evidence)	Latest search completed March 2010	Children (age NR)	GRADE	**TT + Adenoidectomy vs. Adenoidectomy alone** Evidence base: 1 SR Outcomes by-ear: Hearing up to 5 years post-intervention	***Efficacy:*** **TT + Adenoidectomy vs. Adenoidectomy alone** • Combination treatment with ventilation tubes plus adenoidectomy may be more effective than adenoidectomy alone at improving hearing at 1 to 12 months, but effectiveness is unclear at 2 and 5 years post-intervention.

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
				TT vs. No treatment Evidence base: 1 SR Outcomes by-ear: Hearing up to 5 years post-intervention Outcomes by-children: Hearing up to 6 months post-intervention Proportion of time spent with effusion, 1 year after surgery Language comprehension, 6 to 9 months Expressive language, 6 to 9 months Cognition, up to 22 months Outcomes, population not defined: Tympanosclerosis, 1 year Tympanic membrane abnormalities, 3 to 4 years Retraction or atrophy, up to 1 year Perforation, up to 1 year Otorrhea, up to 1 year	**TT vs. No treatment** • Unilateral TT may be effective at improving hearing at 2 years, but effectiveness at 5 years is unclear. • Bilateral TT may be effective at improving hearing at 6 months and reducing the proportion of time spent with effusion in the year after surgery. • The effectiveness of bilateral TT to improve language comprehension or expressive language is unknown at 6 to 9 months • The effectiveness of bilateral TT to improve cognition is unknown at up to 22 months. ***Safety:*** **TT + Adenoidectomy vs. Adenoidectomy alone** • NR **TT vs. No treatment/watchful waiting** • TT may be associated with an increased risk of tympanosclerosis at 1 year and tympanic membrane abnormalities at 3 to 4 years. • The effect of TT on retraction or atrophy, perforation, or otorrhea at up to 1 year is unknown.
Simpson (2007)[8] (Cochrane)	Latest search completed June 30, 2009	Children 0-4 years old identified through screening for	Cochrane Handbook for Systematic Reviews	**TT vs. WW** Evidence base: 1 RCT; SoE NR† Outcomes: Language development	***Efficacy:*** **TT vs. WW:** • The effect of screening and treatment with ventilation tubes on group average hearing levels was evident at six-month follow up,

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
		OME		as measured by Reynell test Change in expressive language levels by the Schlichting test Change in expressive language levels by Lexi Test **TT vs. No Treatment** <u>Evidence base:</u> 1 RCT; SoE NR <u>Outcomes:</u> Language development as measured by Reynell test **Early vs. Late TT Insertion** <u>Evidence base:</u> 5 RCTs; SoE NR <u>Outcomes:</u> Cognition as measured by four different tests Parent-child stress as measured by three different tests Intelligence as measured by the Wechsler Intelligence Scale for Children Language development	but the benefit disappeared by one-year. **TT vs. No Treatment:** • No significant differences in language development were found over six months. **Early vs. Late TT Insertion:** • There were no significant differences between early or late TT treatment groups on any of the study measures for hearing improvement. (Paradise trials) ***<u>Safety:</u>*** • NR for all.
Rovers (2005)[7]	Latest search completed June 2004	Children 0-12 years old	NR	**TT vs. Watchful Waiting** <u>Evidence base by-child:</u> For mean hearing level,	***<u>Efficacy:</u>*** **TT vs. Watchful Waiting** • During a follow up period of 12 months,

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
				4 trials; N = 557 Outcomes by-child: Mean hearing level (dB) at 0, 6, 12, and 18 months post-intervention Language development Mean language development after 6/9 or 12/18 months post-intervention **Functioning TT vs. Nonfunctioning TT or No TT** Evidence base by-child: NR Outcomes by-child: Hearing level, 6 and 12 months post-intervention **TT vs. No TT, by-ear** Evidence base by-ear: 3 RCTs; N = 160 patients Outcomes by-ear: Mean hearing level, 6 and 12 months post-intervention	the mean time spent with effusion was 19.7 weeks (95% CI 17.6 to 21.9) in the children treated with ventilation tubes and 37 weeks (95% CI 34.9 to 39.1) in the watchful waiting group (p=0.0001). • At 6 months follow up the mean hearing level in children treated with ventilation tubes was 26.6 dB HL (SE 1.0) compared to 31.1 dB HL (SE 1.0) in the watchful waiting group (p=0.001). At 12 and 18 months follow up, no differences were found. • No differences were found for language development in children treated with ventilation tubes and the children in the watchful waiting group at 6–9 and 12–18 months follow up (p=0.09 and p=0.19, respectively). • Children with more than one risk factor—including status of day-care attendance, gender, and season— appeared to benefit slight more from treatment with ventilation tubes, but the accumulation was only weak, like most of the individual risk factors. **Functioning TT vs. Nonfunctioning TT or No TT** • Large significant effects on hearing level were found; the mean hearing level in children treated with functioning tubes was about 6 dB HL better compared to children with non-functioning tubes, both after 6 and 12 months follow up (p = 0.0001). • No significant interaction effects indicating relevant subgroups were found.

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
					TT vs. No TT, by-ear • TT appears to be differentially effective in ears with a worse baseline hearing level. • However, if hearing level at baseline was dichotomized at various cut-off values, only a cut-off of 25 dB HL showed an effect. • After 6 months follow-up, ears treated with ventilation tubes and a baseline hearing loss of 25 dB HL or greater improved 10 dB HL more than ears with a similar baseline hearing loss but which were not treated with ventilation tubes. • The ears of children treated with TT and a baseline hearing loss smaller than 25 dB HL improved only 4 dB HL more than the control ears (p 0 0.05 for interaction) • After 12 months follow-up, ears treated with TT and a baseline hearing loss of 25 dB HL or greater improved 7 dB HL more than ears with a similar baseline hearing loss but which were not treated with TT • The ears of children treated with TT and a baseline hearing loss smaller than 25 dB HL improved only 3 dB HL more than the control ears (p = 0.28 for interaction). ***Safety:*** • NR for all
AOM					
Cheong (2012)[30]	January 1990 – March 2011	Children 0-14 years old	NR	**TT vs. Control** Evidence base:	***Efficacy:*** **TT vs. Control and TT vs. Placebo**

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
				2 RCTs; N = 467 Outcome: Patients with no recurrent OM (%) Number of recurrent OM episodes 2 years post-intervention **TT vs. Placebo** Evidence base: 1 RCT; N NR Outcomes: Number of OM episodes 2 years post-intervention Total time with OM 2 years post-intervention	• Tympanostomy tube insertion increases the prevalence of OM re-occurrence. • Tympanostomy tube insertion reduces OM frequency compared to the control or placebo group. ***Safety:*** • NR for all
Damoiseaux (2011)[36] (BMJ Clinical Evidence)	September 1966 – 2010	Children (age NR)	GRADE	**TT vs. No Surgery or Myringotomy Alone** Evidence base: 3 studies, study type NR; = 192 Outcomes: Proportion of children with at least 1 episode of AOM, 6 months post-intervention Mean number of episodes of AOM, 6 and 18 months post-intervention Recurrent ear infections Patients developing tympanosclerosis (%)	***Efficacy:*** **TT vs. No Surgery or Myringotomy Alone** • Tympanostomy tube insertion leads to short-term reduction in the number of episodes of AOM (limited evidence). ***Safety:*** **TT vs. No Surgery or Myringotomy Alone** • Insertion of tympanostomy tubes carries an increased risk of tympanosclerosis. • Tympanostomy tube insertion may increase the risk of tympanosclerosis and hearing impairment.
Lous (2011)[5]	Latest search completed	Children 0-16 years old	NR	**TT vs. Antibiotics** Evidence base:	***Efficacy:*** **TT vs. Antibiotics**

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
	October 2010			2 randomized studies; N = 329 Outcomes: % patients without AOM 6 and 12 months post-intervention **TT vs. Myringotomy** Evidence base, by-ears: 1 randomized study; N = 88 ears Outcomes: Attacks of AOM, 6 months post-intervention **TT vs. Observation Only** Evidence base: 1 randomized study; N = 68 Outcomes: % patients without AOM 6 months post-intervention **TT vs. Placebo** Evidence base: 1 randomized study; N = 264 Outcomes: % patients without AOM 6 months post-intervention **TT vs. No Treatment** Evidence base, by-ears:	• Insertion of tympanostomy tubes or long-term treatment with antibiotics appears to prevent one attack of AOM, or keep one of three free from AOM in six months. • Six month treatment with antibiotics was not different from treatment with tubes, but long-term effect of treatment with amoxicillin seems to be better than treatment with ventilation tubes. **TT vs. Myringotomy** • Ears treated with tubes had 1.2 fewer attacks of AOM in the first six months after treatment (95% CI 0.2 – 2.2) compared with ears without treatment. **TT vs. Observation Only** • NR **TT vs. Placebo** • Treatment with tubes resulted in 61 fewer days with OM in two years compared with placebo. **TT vs. No Treatment** • NR ***Safety:*** • NR for all

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
				1 randomized study; N = 88 ears Outcomes, by-ears: Attacks of AOM, 6 months post-intervention	
McDonald (2011)[6] (Cochrane)	Latest search completed January 11, 2011	Children 0-16 years old	Quality assessment methods as outlined in the Cochrane Handbook for Systematic Reviews	**TT vs. No Treatment** Evidence base: 1 RCT; N = 95 Outcomes Number of episodes of AOM **TT vs. Prophylactic Antibiotics** Evidence base: 1 RCT; N = 68 Outcomes: Number of episodes of AOM	***Efficacy:*** **TT vs. No Treatment** • The difference between children who had no episodes of AOM in the two groups was significant at P < 0.001, suggesting a highly significant role for grommets in maintaining a "disease-free" state. • Grommet insertion leads to a mean reduction of 1.5 episodes of AOM in the first six months after treatment (a reduction of approximately 70%). • Grommet insertion leads to a significant increase in the proportion of children with no episodes of AOM (P < 0.001) (1 RCT, n = 95). **TT vs. Prophylactic Antibiotics** • The difference between children who had no episodes of AOM in the two groups leaned towards grommets as useful in maintaining a disease-free state. • A higher proportion of patients in the grommet group had no episodes of AOM in the six months after intervention, but the difference did not reach statistical significance (P = 0.16) (1 RCT; n = 53).

Author (year)	Search Dates	Population	Critical Appraisal	Evidence Base and Outcomes	Conclusions
					Safety: • NR for all

AOM: Acute otitis media; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; NR: not reported; nonRTC: nonrandomized controlled trial; OME: otitis media with effusion; QoL: Quality of Life; RCT: Randomized controlled trial; rAOM: Recurrent Acute Otitis Media; TT: Tympanostomy tubes, also called ventilation tubes; VT: Ventilation Tubes; WW: Watchful Waiting

* "No TT" is defined as myringotomy alone for temporary effusion drainage without insertion of TT, hearing aids, and WW.

† All patients were from developed countries, authors note that "Evidence generated in the developed world, where children may enjoy better nutrition, better living conditions and less severe and different infections, may not be applicable to children in developing countries."

2.6. Medicare and Representative Private Insurer Coverage Policies

Payer websites were searched for coverage decisions on the use of tympanostomy tubes for treating children with otitis media. Four policies were identified for selected bell weather payers. Coverage policies are consistent for coverage of tympanostomy tube insertion for chronic otitis media with effusion (OME) and recurrent acute otitis media (AOM).

Coverage decisions are summarized briefly below and policy details are provided in Table 5.

Centers for Medicare and Medicaid Services:
There are currently no National Coverage Decisions published from the Centers for Medicare and Medicaid services.

Aetna Clinical Policy Bulletin: Myringotomy and Tympanostomy Tube
Aetna considers myringotomy and tympanostomy tube insertion medically necessary for prolonged OME, recurrent AOM and a variety of other otic problems including cholesteatoma, autophony, severe otalgia and more (see Table 5). Tympanostomy tube insertion for children not classified as previously described, or the use of phosphorylcholine or vancomycin-coated tympanostomy tubes, is considered both experimental and investigational due to lack of effectiveness having been established. Finally, tympanostomy tube insertion is considered not medically necessary for children with a single episode of OME less than three months duration nor those with recurrent AOM without middle ear effusion at time of assessment for candidacy.

Mountain State Blue Cross Blue Shield (A Highmark Affiliate) General Policy Guidelines Topic: Insertion and Removal of Tympanic Ventilation Tubes
Mountain State BCBS reports that a myringotomy may be performed with or without tympanostomy tubes, and that removal of tubes may be paid when under general anesthesia. Removal of tubes is considered an integral part of a doctor's medical care when not performed under general anesthesia, and as such is not eligible as a distinct and separate service.

Oregon Health Authority Health Evidence Review Commission- Coverage Guidance: Management of Chronic Otitis Media with Effusion in Children
Oregon Health Authority HERC states that for the management of chronic OME there should be a 3 to 6 month watchful waiting period after diagnosis of OME, and if persistent hearing loss is ≥25 dB in the better hearing ear, tympanostomy tubes surgery may be covered, given short, but not long term improvement in hearing.

Oregon Health Authority Health Evidence Review Commission- Coverage Guidance: Management of Acute Otitis Media in Children
Tympanostomy tubes may be covered for AOM only for recurrent AOM, defined as three or more episodes in six months or four or more episodes in one year.

Table 5. Overview of payer technology assessments and policies for tympanostomy tubes

Payer (year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Centers for Medicare and Medicaid Services	NA	NA	None	There are currently no National Coverage Decisions (NCDs) published from the Centers for Medicare and Medicaid Services.
Aetna *Clinical Policy Bulletin: Myringotomy and Tympanostomy Tube* POLICY #: 0418 Effective Date: 05/04/2000 Last Review Date: 06/10/2014 Next Review Date: 04/23/2015	NR	60 studies, clinical guidelines, books, randomized controlled trials, systematic reviews/meta-analyses, health technology assessments and review papers	Aetna considers myringotomy and tympanostomy tube (also known as ventilation tube and grommet) insertion medically necessary for any of the following indications: 1. Autophony due to patulous Eustachian tube; or 2. Barotitis media control; or 3. Cholesteatoma; or 4. Chronic retraction of tympanic membrane or pars flaccida; or 5. Complications of otitis media such as meningitis, facial nerve paralysis, coalescent mastoiditis, or brain abscess; or 6. Otitis media with effusion after 3 months or longer and bilateral hearing impairment (defined as 20 dB hearing threshold level or worse in both ears) (tympanostomy tube); or 7. Recurrent episodes of acute otitis media (more than 3 episodes in 6 months or more than 4 episodes in 12 months) (tympanostomy tube); or 8. Severe otalgia in acute otitis media (myringotomy); or 9. To obtain a culture (diagnostic	NR

Payer (year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
			tympanocentesis/myringotomy) of the middle ear fluid prior to beginning or changing antimicrobial therapy (this may be necessary in situations such as otitis media that has failed to respond to appropriate antimicrobial therapy, or for otitis media in individuals or neonates who are immunocompromised). Tympanostomy tube insertion is considered not medically necessary for children with: • A single episode of otitis media with effusion (OME) of less than 3 months' duration. • Recurrent acute otitis media (AOM) who do not have middle ear effusion in either ear at the time of assessment for tube candidacy. Aetna considers myringotomy and tympanostomy tube insertion experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established. Aetna considers the use of (i) phosphorylcholine-coated tympanostomy tube and (ii) vancomycin-coated tympanostomy tube experimental and investigational because their effectiveness has not been established.	
Mountain State Blue Cross Blue Shield (A Highmark Affiliate) *General Policy Guidelines Topic: Insertion and Removal of Tympanic Ventilation Tubes* Number: S-30	NR	2 clinical practice guidelines, 6 SRs, 2 meta-analyses, 1 review	• A myringotomy (69420, 69421, or S2225) may be performed with or without the insertion of tympanostomy tubes. Insertion of tubes should be reported under code 69433 or 69436, as appropriate. • Removal of ventilation, myringotomy, or tympanostomy tubes (i.e., Shea or Collar button) may be paid when performed under general	NR

Payer (year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Effective Date: August 1, 2005 Issued Date: 01/30/2006 Date Last Reviewed: 01/2006			anesthesia (69424). • However, removal of such tubes is considered an integral part of a doctor's medical care when not performed under general anesthesia, and therefore, is not eligible as a distinct and separate service.	
Oregon Health Authority Health Evidence Review Commission (HERC) *Coverage Guidance: Management of Chronic Otitis Media With Effusion in Children* Date: 10/11/2012	NR	NR	For the management of chronic otitis media with effusion in children: • There should be a 3 to 6 month watchful waiting period after diagnosis of otitis media with effusion, and if the documented persistent hearing loss is greater than or equal to 25dB in the better hearing ear, referral for tympanostomy surgery may be covered, given short, but not long-term, improvement in hearing.	NR
Oregon Health Authority Health Evidence Review Commission (HERC) *Coverage Guidance: Management of Acute Otitis Media in Children* Date: 08/08/2013	NR	1 systematic review, 1 AHRQ HTA	• Tympanostomy tubes may be covered for acute otitis media only for recurrent acute otitis media.	Recurrent otitis media is defined here as three or more episodes in six months or four or more episodes in one year.

3. The Evidence

3.1. Methods of the Systematic Literature Review

3.1.1. Objectives

The objective of this Health Technology Assessment was to systematically review, critically appraise, analyze and synthesize research evidence evaluating the comparative efficacy, effectiveness, and safety of tympanostomy tubes in children for treating otitis media with or without effusion. The differential effectiveness and safety of tympanostomy tubes for subpopulations was evaluated, as was the cost effectiveness.

Key Questions:

In children aged 16 years and younger with either (a) chronic otitis media with effusion (OME) or (b) recurrent or persistent acute otitis media (AOM) (evaluated separately):

1. What is the evidence of the short- and long-term efficacy and effectiveness of tympanostomy tube insertion compared with alternative treatment options or watchful waiting? Under what circumstances are tympanostomy tubes indicated?
2. What is the evidence regarding short- and long-term harms and complications of placement of tympanostomy tubes compared with alternative treatment options or watchful waiting?
3. Is there evidence of differential efficacy, effectiveness, or safety of tympanostomy tubes compared with alternative treatment options or watchful waiting? Include consideration of age, sex, race, ethnicity, socioeconomic status, risk for developmental delay, repeated exposure to large groups of children, duration of otitis media, and recurrent acute versus chronic otitis media.
4. What is the evidence of cost-effectiveness of tympanostomy tubes compared with alternative treatment options?

3.1.2. Inclusion/exclusion

The inclusion and exclusion criteria are summarized in Table 6.

- Population: Studies of children age 16 and younger who received tympanostomy tube (TT) insertion for either chronic otitis media with effusion (OME) or recurrent acute otitis media (AOM).
- Intervention: Included studies evaluated tympanostomy tubes.
- Comparators: Included studies compared TTs to watchful waiting (with or without delayed TT insertion), myringotomy, adenoidectomy, antibiotic therapy, mucolytics, steroids, autoinflation of the Eustachian tube, or complementary and alternative medicine treatments.
- Outcomes: Eligible studies reported on at least one of the following outcomes: hearing, otorrhea, recurrent AOM, recurrent OME, balance and coordination, cholesteatoma, attention and behavioral outcomes, academic achievement, auditory processing, speech and language development, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, patient quality of life, parent quality of life, pain, surgery, medication usage, number of office visits, or harms (including harms of TT, comparator treatment, or general anesthesia (see Table 6 for details)).
- Study design: Eligible studies compared TT with an included comparator treatment utilizing a randomized or cohort study design; nonrandomized comparative retrospective studies were considered if they included at least 100 patients and had complete follow-up of at least 80% of patients. Case series specifically designed to

evaluate harms/adverse events that enrolled at least 500 patients and that had follow-up of at least 70% of patients were considered for Key Question 2. Only RCTs were considered for Key Question 3; subpopulations of interest are listed in Table 6. For Key question 4, formal economic analyses were eligible for inclusion; the emphasis was placed on studies based on patient outcomes (rather than those that used a hypothetical patient cohort).

Table 6. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Children age 16 and younger with either: (a) chronic otitis media with effusion (OME), or (b) recurrent or persistent acute otitis media (AOM) (evaluated separately)	• Patients aged 17 and older
Intervention	Tympanostomy tube insertion	• Devices that have not received FDA-approval
Comparator	• Watchful waiting with or without delayed tympanostomy tube insertion • Alternative disease-appropriate treatments, including: – Antibiotic therapy (systemic or topical antibiotics) – Other medications (mucolytics, oral or intranasal steroids) – Myringotomy alone – Adenoidectomy – Autoinflation of the Eustachian tube – Complementary and alternative medicine treatments	• Antihistamines • Decongestants • Devices or interventions that have not received FDA-approval
Outcomes	**<u>Efficacy/effectiveness</u>** (*indicates primary outcome) **OME:** *Clinical outcomes* • Hearing loss*† • Otorrhea* • Recurrent AOM • Balance and coordination (vestibular function) • Recurrent OME • Cholesteatoma*† *Functional and quality of life outcomes* • Attention and behavioral outcomes* • Academic achievement* • Auditory processing* • Speech and language development*† • Parent satisfaction with treatment/outcomes*† • Patient quality of life*† • Pain	• Non-clinical outcomes • For Key Question 4, costing only.

Study Component	Inclusion	Exclusion
	• Parental quality of life • Patient satisfaction with treatment/outcomes *Healthcare utilization* • Surgery* • Medication usage • Number of office visits **AOM** *Clinical outcomes* • Hearing loss*† • Recurrent AOM • Balance and coordination (vestibular function) • Otorrhea • Recurrent OME • Cholesteatoma *Functional and quality of life outcomes* • Parent satisfaction with treatment/outcomes*† • Patient quality of life*† • Attention and behavioral outcomes • Academic achievement • Auditory processing • Speech and language development • Pain • Parental quality of life • Patient satisfaction with treatment/outcomes *Healthcare utilization* • Surgery* • Medication usage • Number of office visits **<u>Harms</u>** • Treatment related harms, including: – Harms of tympanostomy tubes (e.g., chronic otorrhea†, blockage of the tympanostomy tube lumen, premature tube extrusion, tube displacement into middle ear, tympanosclerosis/ myringosclerosis; or tympanic membrane atrophy, atelectasis, retraction pocket formation, or perforation†) – Harms of general anesthesia (e.g., death, laryngospasm,	

Study Component	Inclusion	Exclusion
	bronchospasm) – Harms of alternative treatment options (e.g., adverse effects of antibiotics‡, suppurative complications§, etc.) **Cost-effectiveness** • Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER)) outcomes	
Study Design	Focus will be on studies with the least potential for bias. **Key Questions 1-3:** • High quality systematic reviews will be considered if available. • Randomized controlled trials (RCTs) and non-randomized comparative prospective studies will be sought. Nonrandomized comparative retrospective studies with N≥100 and ≥80% complete follow-up were also included. **Key Question 2:** • KQ2: High-quality case series (non-comparative studies) designed specifically to evaluate harms/adverse events and that included N≥500 and had ≥70% complete follow-up were also included. **Key Question 3:** Studies which stratify on patient or other characteristics and formally evaluate statistical interaction (effect modification). Subgroups of interest include: • Otitis media duration • Recurrent acute versus chronic otitis media • Children at risk for developmental disabilities, including: – Permanent hearing loss (independent of otitis media) (including sensorineural hearing loss) – Speech and/or language delay or disorder – Autism spectrum disorders – Down Syndrome – Craniofacial disorders (e.g., cleft palate) that are associated with cognitive, speech, and/or language delays – Blindness or uncorrectable visual impairment – Developmental delay • Age • Sex • Repeated exposure to large groups of children (e.g., daycare, etc.) • Race • Socioeconomic status	• Indirect comparisons • Noncomparative studies (case series) (except as described to evaluate harms) • Incomplete economic evaluations such as costing studies • Studies with fewer than 10 patients • Case reports

Study Component	Inclusion	Exclusion
	Key Question 4: • Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered; those that based the analysis on patient outcomes data were sought; those that used hypothetical patient cohort(s) were briefly summarized.	
Publication	• Studies published in English in peer reviewed journals or publically available FDA reports	• Abstracts, editorials, letters • Duplicate publications of the same study which do not report on different outcomes • Single reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions

* Primary outcome

† Critical outcome

‡ Harms of antibiotics may include increased bacteria resistance, rash, and diaper dermatitis.

§ Suppurative complications may include damage to tympanic membrane, facial nerve paralysis, meningitis, brain abscess, otitic hydrocephalus, mastoiditis, and lateral sinus thrombosis

3.1.3. Critical and primary outcomes

The greatest emphasis was placed outcomes that are directly related to the health outcomes of patient; outcomes of interest are listed in Table 6. The primary outcomes of interest were also identified based on clinical expert input. Specifically, the clinicians were asked to rank each outcome based on the level of importance on a scale of 1-9, with higher scores indicating greater importance. Those outcomes that were either (a) were ranked 7-9 by all three clinicians or (b) had an average ranking of 7-9 were selected as primary outcomes. Because of the large number of resulting primary outcomes, critical outcomes were then selected based on clinical expert input as those which were of critical importance for making a policy decision; the overall strength of evidence (SoE) was formally evaluated for these critical outcomes.

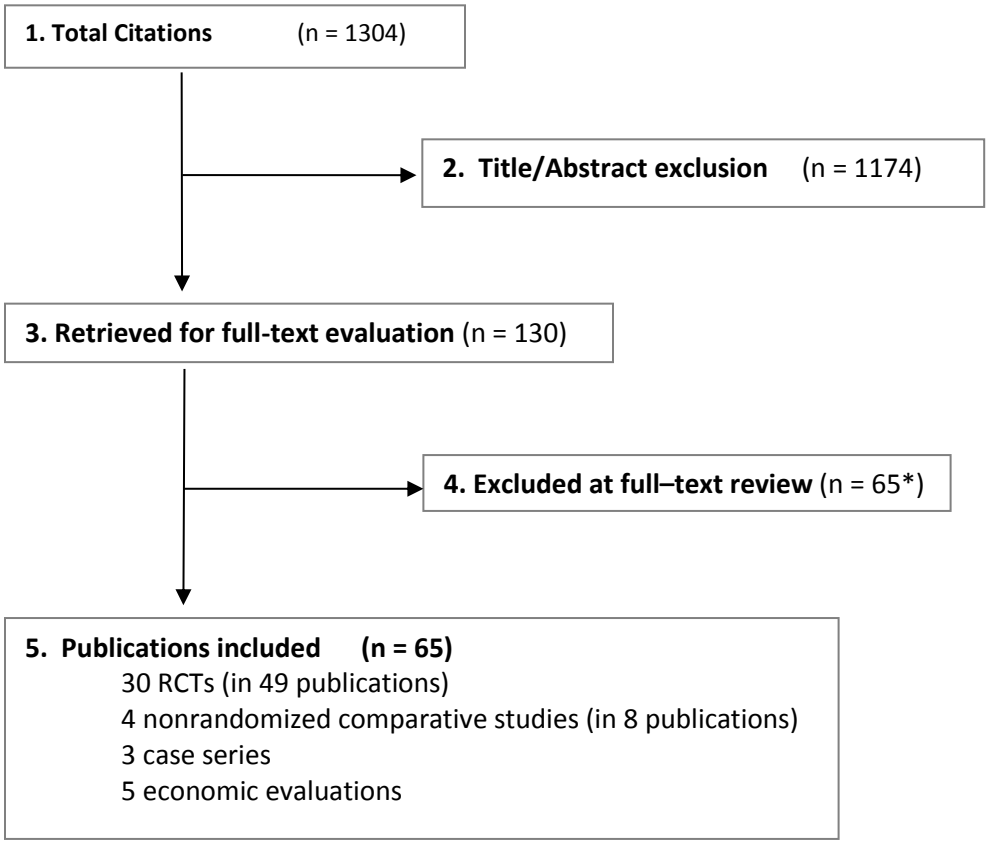
3.1.4. Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. All possible relevant articles were screened using titles and abstracts in stage two. This was done by one to two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were

included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of a priori inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

Electronic databases were searched from their inception through February 3, 2015. Electronic databases searched included PubMed, EMBASE, and AHRQ for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. The search strategies used for PubMed are shown in Appendix B. Figure 2 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed with reason for exclusion in Appendix C.

Figure 2. Flow chart of literature search results



* Studies listed with reason for exclusion in Appendix C

3.1.5. Data extraction

Reviewers extracted the following data from the studies included to address Key Questions 1-3: study design, inclusion/exclusion criteria, country and number of centers, funding source, inclusion/exclusion criteria, criteria used for diagnosis of OME and/or AOM, demographics, and results. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Detailed study characteristics are available in Appendix F, demographics and intervention details are presented in the results section (Tables 7-28), and results in Appendices G and H.

3.1.6. Quality assessment: Overall Strength of evidence (SoE), Class of evidence (CoE) and QHES evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine,[122] precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,[5] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[172] Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[111] Details of the CoE and QHES methodology are available in Appendix D. Based on these quality criteria, each study chosen for inclusion for a Key Question was given a CoE (or QHES) rating; details of each rating are available in Appendix E. Standardized abstraction guidelines were used to determine the CoE (or QHES) rating for each study included in this assessment. Studies were considered to have been conducted retrospectively unless clearly stated otherwise.

The strength of evidence for the overall body of evidence for all critical health outcomes was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ).[9] The strength of evidence was based on the highest quality evidence available for a given outcome. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results that are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.
- Publication bias: is considered when there is concern of selective publishing.

Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association). The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- High - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- Moderate – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- Low – Limited confidence that effect size estimates lie close to the true effect for this outcome; major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or that the estimate is close to the true effect.
- Insufficient – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 4 was not assessed.

3.1.7. Analysis

For Key Questions 1 to 2, an attempt was made to pool results when there were two or more RCTs of similar quality and that employed similar interventions and outcome timing/interpretation. However, because of differences in study quality, RCTs were not pooled with nonrandomized studies. For all dichotomous outcomes, risk differences were calculated to compare the rate of occurrence between treatments. For dichotomous outcomes that could be pooled, risk differences and figures were produced using Review Manager v5.2.6 and the difference within each study was weighted and pooled the Mantel-Haenszel method. For outcomes that could not be pooled, risk differences were calculated using the Rothman Episheet (www.krothman.org/episheet.xls). For all continuous outcomes, mean differences (MD) and their respective 95% confidence intervals were calculated. For outcomes that could be pooled, mean differences were weighted accord to the inverse of their variance; results and figures were produced using Review Manager v5.2.6. In some instances, when a study (Black) did not report effect sizes for individual treatments, the standard error was computed using the available confidence intervals. The more conservative random effects model was assumed to account for inter-study variability. Effect sizes were reported and displayed along with their respective 95% confidence intervals. For continuous outcomes that could not be pooled, mean differences and their respective 95% confidence intervals were calculated using GraphPad Software's unpaired t test (http://graphpad.com/quickcalcs/ttest1/?Format=SD).

4. Results

4.1. Key Question 1: Efficacy and effectiveness, indications

4.1.1. Number of studies retained

This review focused on RCTs and non-randomized prospective cohort studies. Retrospective cohort studies with at least 100 patients and 80% follow-up were also considered for inclusion. Of the 110 comparative publications that underwent full-text review, 30 RCTs (reported across 49 publications), 3 prospective cohort studies (reported across 7 publications), and 1 retrospective cohort study were included in the report; the remaining 53 publications were excluded after full text review (see Appendix C). Study and intervention characteristics are provided in Tables 7-28 and additional information, including inclusion and exclusion criteria as well as study funding, is available in Appendix F.

Results are presented by disease (OME or AOM) and sorted by comparator treatments identified: watchful waiting, myringotomy, myringotomy plus adenoidectomy, adenoidectomy (with or without tonsillectomy), and antibiotics. There was no evidence identified on any of the other included comparator treatments (i.e., mucolytics, autoinflation of the Eustachian tube, complementary and alternative medicine treatments).

Although an attempt was made to stratify results by age at treatment, the mean age did not vary considerably between studies of the same comparators. Mean patient age is included for each study throughout the results section.

4.1.2. OME: Tubes versus watchful waiting (WW) or no surgery (by-child analysis)

Studies included

Seven RCTs reported across 20 publications[59,67,70,88,89,95,98-100,114-118,127,139-141,173,177] were identified for inclusion. No cohort studies met the inclusion criteria. For this comparison, studies which compared tympanostomy tube (TT) insertion to watchful waiting, active monitoring, delayed TT insertion, or no treatment were sought. By design, this comparison is only applicable to studies that performed by-child analysis (rather than by-ear analysis). Note that studies comparing unilateral TT to no surgery in the contralateral ear are included in section 4.1.2; this is because in that situation, all children underwent surgery, which is inherently different than a child receiving no surgery at all.

Study characteristics

The included trials were published between the years 1989 and 2012 and enrolled between 52 and 429 patients. Mean patient age ranged from 1.25 to 5.2 years across five of the trials (COMET[59,95,173], Paradise[70,114-118], Rovers[67,139-141], TARGET[98,100], Rach[127,177]); two trials[88,89,139] (Mandel 1989[88], Mandel 1992[89]) reported only that patients ranged in age from 0.6 to 12 years. Across the trials, 29% to 52% of patients were females. Four trials only included patients with bilateral OME (COMET[59,95,173], Rovers[67,139-141], TARGET[98,100], Rach[127,177]), and three trials included patients with either unilateral or bilateral OME (Paradise[70,114-118], Mandel 1989[88], Mandel 1992[89]). Hearing loss was required for inclusion in three of the trials (COMET[59,95,173], Rovers[67,139-141], TARGET[98,100]); one trial did not require hearing loss but reported that 71.5% of patients had hearing loss at baseline (Paradise[70,114-118]); and three trials did not require hearing loss but did not report baseline hearing levels (Rach[127,177], Mandel 1989[88], Mandel 1992[89]), one of which required that hearing levels not be greater than 35 dB (Mandel 1992[89]). One trial required that patients have disrupted speech, language, or behavior for inclusion (COMET[59,95,173]), otherwise, no other

trials required any additional symptoms for inclusion. Study characteristics, including quality assessment ratings, are summarized in Table 7.

Intervention details are summarized in Table 8. Briefly, patients randomized to receive tympanostomy tubes (TT) were treated with general anesthesia. Some trials did not specify the use of general anesthesia, however, there was no indication otherwise. In general, patients received a tube in the affected ear; one trial (COMET[59,95,173]) noted that patients could undergo simultaneous adenoidectomy if indicated, but no other details were reported. Tube reinsertion was commonly permitted; see Table 8 for details. Protocols were more varied between trials for those randomized to watchful waiting (WW) or delayed treatment; in general, little detail was given. Two trials (COMET[59,95,173], Paradise[70,114-118]) included a formal reassessment for tube insertion at six to nine months; the COMET trial allowed tubes to be inserted in WW patients who had persistent bilateral OME and parental concerns about worsening in hearing, language, or behavior; the Paradise trial did not report requirements for tube insertion in WW patients but did note that tubes could be inserted at any time upon parental request (even before the scheduled reassessment). One additional trial (TARGET[98,100]) permitted tube insertion at any time at parental request. One trial specified that no treatment was given unless tubes were indicated (Mandel 1989[88]) and three trials gave no details about the WW group (Rovers[67,139-141], Mandel 1992[89], Rach[127,177]). Tube insertion and reinsertion rates varied across trials; see Table 8 for details.

Table 7. Study characteristics and patient demographics: TT vs. WW or no treatment for OME

Study	N	Interventions (n)	OME	Hearing Loss	Additional Symptoms Required	Age Range (mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
COMET 1999, 2000, 2009[59,95,173]	182	• Bilateral TT* (n=92) • WW/delayed TT (n=90)	Bilateral (consecutive appointments 3 months apart)	Hearing loss required (25-70dB) for ≥ 3 mos.	Disrupted speech, language, or behavior	1.2 – 4.7 (mean 2.9) yrs.	52%	-	9 mos. (92%) 18 mos. (86%) Age 4.5 yrs. (75%) Age 7-8 yrs. (59%/86%†)	CoE I
Paradise 2001, 2003, 2005, 2007, Johnston 2004[70,114-118]	429	• Unilateral or bilateral TT • (n=216) • WW/delayed TT (n=213)	Bilateral‡: ≥ 3 months (37%) -or- Unilateral‡: ≥ 4.5 months (63%)	Not required (≥20dB on ≥1 test in 71.5% of patients)	-	0.2 – 3 (mean 1.25) yrs.	43%	-	Age 3 yrs. (94%) Age 4 yrs. (93%) Age 6 yrs. (92%) Age 9-11 yrs. (91%)	CoE I
Rovers 2000, 2001, Ingels 2005[67,139-141]	206	• Bilateral TT • (n=108) • WW/delayed TT (n=98)	Bilateral (4 – 6 months)	Hearing loss required (≥35 dB at 3rd test in 3 mos.)	-	Infants (mean 1.6 yrs.§)	41%**	-	3 mos. (NR) 6 mos. (85%) 9 mos. (NR) 12 mos. (85%)	CoE III
TARGET 2003, 2012[98,100]	376††	• Bilateral TT • (n=126) • WW/delayed TT (n=122)	Bilateral (≥ 3 months)	Hearing loss required (≥20dB)	-	3.5 – 7 (mean 5.2) yrs.	51%	-	3 mos. (NR) 6 mos. (NR) 12 mos. (NR) 18 mos. (NR) 24 mos. (85%)	CoE II
Mandel 1989[88] (no hearing loss group only‡‡)	86	• TT • (n=30) • WW/delayed surgery (n=29) • (Myringotomy n=27)	Bilateral (64%) or unilateral (36%) (≥ 2 months)	No significant hearing loss (≤20dB if bilateral or ≤40dB if unilateral)	-	0.6 – 12 yrs. (NR§§)	29%	-	2 mos. (NR) 12 mos. (NR) 24 mos. (NR) 36 mos. (85%***)	CoE III

Study	N	Interventions (n)	OME	Hearing Loss	Additional Symptoms Required	Age Range (mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
Mandel 1992[89]	111	• TT (n=37) • WW/delayed surgery (n=35) • (Myringotomy n=39)	Bilateral (59%) or unilateral (41%) (≥ 2 months)	Not required, hearing level ≤35 dB	-	0.6 – 12 yrs. (NR§§)	33%	-	12 mos. (NR) 24 mos. (NR) 36 mos. (87%)	CoE III
Rach 1991, Zielhuis 1989[127,177]	52	• Bilateral TT • (n=22**) • No treatment (n=21**)	Bilateral (consecutive appointments 3 months apart)	Not required (details NR)	-	2 – 4 yrs. (mean 3.3**) yrs.	40%**	-	6 mos. (83%)	CoE III
Cohort Studies										
(none)										

F/U: follow-up; NR: not reported; pop.: population

* COMET (Maw 1999): patients with nasal obstruction due to enlarged adenoids also received adenoidectomy but no patient numbers or additional details were reported

† COMET (Maw 1999): 59% of patients had complete follow-up for all data except SATS results, which were available in 86% of patients.

‡ Paradise 2001: Patients could have either continuous or discontinuous middle ear effusion: bilateral continuous (18%); unilateral continuous (16%); bilateral discontinuous (19%); unilateral discontinuous (47%). Those with discontinuous middle ear effusion were required to have it 67% of the time period specified in the table.

§ Rovers 2000: Age range not clearly defined but appeared to be under 2 years of age.

** Rach 1991, Rovers 2000: data reflects those who completed follow-up only.

†† TARGET (MRC 2012): the tubes + adenoidectomy group (n=128) was excluded from this systematic review as there was no appropriate control to evaluate tubes alone (i.e., adenoidectomy alone) against this treatment.

‡‡ Mandel 1989: A total of 109 patients were enrolled and first stratified according to the absence (n=23) or presence (n=86) of hearing loss ((>20dB bilaterally or >40dB unilaterally or speech awareness threshold >20dB higher than appropriate for age); patients were randomized within these groups to treatments as follows: No hearing loss: Tubes (n=30), no surgery (n=29), myringotomy (n=27); Hearing loss: Tubes (n=11), myringotomy (n=12)

§§ Mandel 1989; Mandel 1992: The following age groups were reported: Mandel 1989: no hearing loss patients (n=111): 24% of patients aged 7-23 months; 56% aged 2-5 years; 20% aged 6 to 12 years. Mandel 1992: 32% of patients aged 7-23 months; 51% aged 2-5 years; 18% aged 6 to 12 years.

*** Mandel 1989: 85% f/u for all 109 patients in study.

Table 8. Intervention details: TT vs. WW or no treatment for OME

Study	Interventions (n)	Treatment Protocol	Indication for Tube (Re)insertion	Tube (Re)insertion (%)
RCTs				
COMET[59,95,173]	TT (n=92)	• Anesthesia NR • Bilateral • Shepard or Shah tubes • Adenoidectomy if indicated (n=NR)	• Return of hearing loss or effusions	• 0-18 mos.: 19% (17/90)
	WW/delayed TT (n=90)	• Reassessment at 9 months; if indicated tubes (with adenoidectomy if indicated) inserted within 6 weeks.	• Persistent bilateral OME and parental concern about worsening in hearing, language, or behavior.	• <9 mos.: 18% (16/90) (against protocol) • 9 mos.: 48% (43/90) • 0-18 mos.: 88% (79/90)
Paradise [70,114-118]	TT (n=216)	• General anesthesia • Unilateral (63%) or bilateral (37%) • Tube type NR	• NR	• NR
	WW/delayed TT (n=213)	• Reassessment at 6 (9) months for bilateral (unilateral) OME; if indicated tubes inserted. • At parent request at any time.	• No additional details reported.	• ≤1 mos.: 2.0% (4/196) • ≤2 mos.: 4.6% (9/196) • ≤6 mos.: 11.2% (22/196) • ≤Age 3: 33.2% (65/196) • ≤Age 4: 38.3% (75/196) • ≤Age 6: 40.3% (79/196) • ≤Age 9-11: 45.0% (88/196)
Rovers[67,139-141]	TT (n=108)	• Anesthesia NR • Bilateral • Bevel Bobbins	• Early tube extrusion (<6 mos.)	• ≤6 mos.: 9% (8/93)
	WW/delayed TT (n=98)	• NR	• NR	• ≤12 mos.: 10% (10/98)
TARGET[98,100]	TT	• General anesthesia	• At parent request	• ≤3 mos.: 0.8% (1/126)

Study	Interventions (n)	Treatment Protocol	Indication for Tube (Re)insertion	Tube (Re)insertion (%)
	(n=126)	• Bilateral • Shepard tubes		• 3-12 mos.: 2.4% (3/126) • 12-24 mos.: 10.3% (13/126) • 0-24 mos.: 12.7% (16/126)
	WW/delayed TT (n=122)	• Tube insertion (± adenoidectomy ± tonsillectomy) within 6 weeks if indicated (details NR).	• At parent request	• ≤3 mos.: 9.8% (12/122) • 3-12 mos.: 33.6% (41/122) • 12-24 mos.: 14.8% (16/122) (plus 2 had reinsertion) • 0-24 mos.: 56.6% (69/122)
Mandel 1989[88]	TT (n=30)	• General anesthesia • Unilateral (30%) or bilateral (70%) • Armstrong tubes	• Bilateral middle ear effusion and significant hearing loss at three consecutive monthly visits (i.e., over 2 months).	• 0-12 mos.: 15% (4/27) • 12-24 mos.: 33% (9/27) • 24-36 mos.: 8% (2/25)
	WW/delayed surgery (n=29)	• No treatment unless tubes indicated	• Same	• 0-12 mos.: 52% (13/25) • 12-24 mos.: 25% (4/16) • 24-36 mos.: 6% (1/16)
Mandel 1992[89]	TT (n=37)	• General anesthesia • Unilateral (43%) or bilateral (57%) • Armstrong tubes	• Treatment failure: Bilateral (unilateral) middle ear effusion persisting for 4 (6) months.	• 0-12 mos.: 3% (1/34) • 12-24 mos.: 23% (7/30) • 24-36 mos.: 21% (6/28)
	WW/delayed surgery (n=35)	• Details NR	• Same	• 0-12 mos.: 56% (19/34) • 12-24 mos.: 33% (11/33) • 24-36 mos.: 28% (8/29)
Rach[127,177]	TT (n=22*)	• General anesthesia • Bilateral • Donaldson tubes	• NR	• NR
	No treatment (n=21*)	• Details NR	• NR	• NR

F/U: follow-up; NR: not reported; pop.: population

* Rach 1991: data reflects those who completed follow-up only.

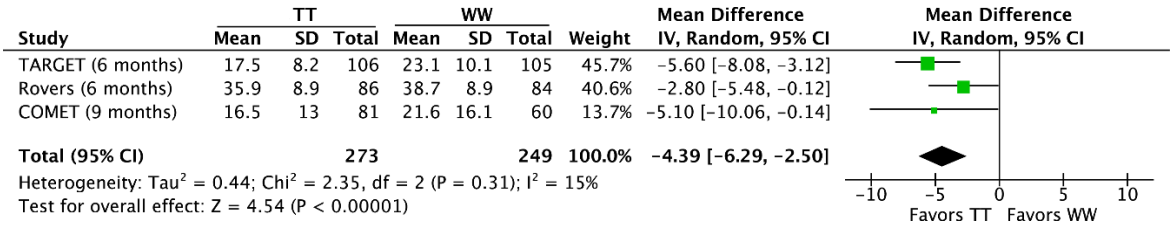
Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G1-G15).

Clinical outcomes

Hearing levels (by child)
Four trials reported hearing levels by child: COMET[59,95,173] (CoE I), TARGET[98,100] (CoE II), Rovers[67,139-141] (CoE III), and Paradise[70,114-118] (CoE I). The majority of patients had hearing loss at baseline. Overall, results suggest a short-term benefit in hearing levels (as measured at six to nine months) but no difference between groups in hearing levels by 12 to 18 months follow-up (three trials). A fourth trial found that hearing levels at age 6 (~36 to 70 months follow-up) were similar between groups.

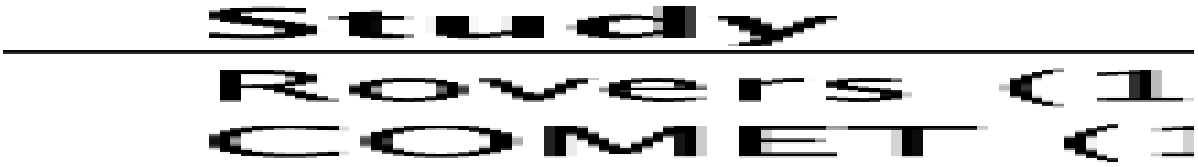
Three RCTs (COMET[59,95,173], TARGET[98,100], Rovers[67,139-141]) were amenable to meta-analysis; all required bilateral OME and hearing loss for inclusion. All patients were 7 years old or younger, with mean age across trials ranging from 1.6 to 5.2 years. Baseline hearing levels were similar between groups: the COMET and TARGET trials had baseline hearing levels that ranged from 33.2 to 38.3 in the TT group and from 33.8 to 39.6 in the WW group; the Rovers trial, which required hearing levels of 35 dB or higher for inclusion, had worse hearing levels at baseline than the other two trials (46.1 vs. 43.2, respectively) (Appendix Table G1). At three months, one trial (TARGET[98,100]) reported better hearing levels in the tubes group (14.4 ± 6.9 dB) than in the WW group (26.3 ± 9.9 dB), mean difference -11.90 (95% CI -14.19 to -9.61) (p<0.001). At six to nine months, results from all three trials individually show that hearing levels are significantly better in the TT group; pooled data suggest an overall mean difference of -4.39 dB (i.e., hearing levels were 4.39 dB lower (better) in the TT group)) (95% CI -6.29 to -2.50 dB, p<0.00001) (Figure 3). Note that by nine months, the following percentage of patients in the WW group had received tubes: <2.4% (TARGET[98,100]), <10% (Rovers[67,139-141]), 66% (59/90) (COMET[59,95,173]).

Figure 3. Hearing levels by patient at 6 to 9 months: TT vs. WW for OME



By 12 to 18 months follow-up, there were no longer significant differences in mean hearing levels between groups in any of the three studies, with a pooled mean difference of -0.45 dB between groups (95% CI, -2.44 to 1.54 dB, p=0.66) (Figure 4). At the end of the study periods (12-18 months), tubes had been placed in 10% (Rovers[67,139-141]), 56.6% (TARGET[98,100]), and 88% (COMET[59,95,173]) of WW patients.

Figure 4. Hearing levels by patient at 12 to 18 months: TT vs. WW for OME



A subset of the Paradise trial (Johnston[70]) also reported mean hearing levels for a subset of patients at age 6 (mean age was 1.25 years (range 0.2 to 3 years) at randomization). At baseline, 71.5% of patients had hearing levels that were 20dB or higher; mean baseline hearing levels were not reported. At age six (~36 to 70 months follow-up), mean hearing levels were not significantly different between TT (6.2 ± 4.1 dB (both ears)) and WW groups (5.5 ± 3.4 (left ear), 6.0 ± 5.5 (right ear)) (p≥0.12) (Appendix Table G1). At age six, 40.3% (79/196) of WW patients had received tubes.

Subanalysis: hearing levels in patients with intact or functioning tubes

Rovers[67,139-141] reported that when the subset of TT patients with functioning tubes was compared to all WW patients, the difference in hearing levels between groups was even more pronounced (6 months (32.5 ± 0.8 (SE) vs. 38.7 ± 1.0 (SE)) (p=0.0001); 12 months (29.9 ± 0.8 (SE) vs. 34.7 ± 0.8 (SE)) (p=0.0003)).

TARGET[98,100] noted that hearing levels were relatively stable in ears with functioning tubes over the entire follow-up and that patients with functioning tubes had better hearing levels than the mean of the entire TT group. At six months, the mean hearing level in the 130 ears with a functioning tube was 12.3 ± 4.9 dB (compared with overall mean hearing levels of 17.5 ± 8.2 in the TT and 23.1 ± 10.1 in the WW group). At twelve months the 45 ears with functioning tubes had a mean hearing level of 13.3 ± 5.7 dB (compared with overall mean hearing levels of 21.0 ± 9.4 2 in the TT and 20.5 ± 10.1 in the WW group). At 18 months, the 32 ears with functioning tubes had a mean hearing level of 16.8 ± 9.6 dB (compared with overall mean hearing levels of 21.1 ± 10.2 in the TT and 20.5 ± 10.1 in the WW group).

Otorrhea

Otorrhea was reported by three trials: Rovers[67,139-141] (CoE III), Mandel 1989[88] (CoE III), and TARGET[98,100] (CoE II). Rovers[67,139-141] (mean age 1.6 years at enrollment) found that parent-reported otorrhea was significantly higher in the TT versus the WW group at each time point through 12 months, through which time a total of 83% of TT versus 38% of WW patients developed otorrhea (RD 45%, 95% CI 32% to 57%, p<0.001) (Appendix Table G2). Interestingly, TARGET[98,100] (mean age 5.2 years) reported a considerably lower incidence of otorrhea (which was not further defined), affecting less than 2% of TT patients (including the 128 patients who received TT + adenoidectomy) and no WW patients through 24 months. It is unclear what may have caused this large discrepancy between trials, but a 2% incidence of otorrhea is unexpectedly low.[134] Mandel 1989[88] (age 0.6 to 12 years at enrollment) reported that otorrhea occurred more frequently in the TT group than the WW group, with 0.41 (TT) versus 0.23 (WW) otorrhea episodes per year over three years, though it was not reported whether the result was statistically significant.

AOM episodes

Two trials reported AOM episodes during follow-up: Mandel 1989[88] (CoE III) and Mandel 1992[89] (CoE III); both trials enrolled children between the ages of 0.6 and 12 years. The number of AOM episodes in the first year was significantly lower in the TT group than the WW group in one trial (0.23 versus 0.95 AOM

episodes per patient, mean difference -0.72) (Mandel 1992[89]). However, both studies found no difference between groups when taking the average number of AOM episodes per year over the first three years (0.18-0.51 (TT) versus 0.38-0.58 (WW) AOM episodes per year, mean difference -0.07 to -0.20) (Appendix Table G3).

AOM or OME recurrence

Three trials reported the percentage of time spent with either AOM or OME (Paradise[70,114-118] trial (CoE I), Mandel 1989[88] (CoE III), Mandel 1992[89] (CoE III)). Overall, results suggest that the frequency of either AOM or OME is lower in the first year of follow-up in the TT versus the WW group as well as cumulatively over three years follow-up. Over the first year of follow-up, patients in the TT group spent 16.4% to 29% of time with AOM or OME, while those in the WW group spent 56.3% to 64% of time with either condition (range of means, p<0.001 for each study) (Paradise[70,114-118], Mandel 1989[88], Mandel 1992[89]). Through the first two (Paradise[70,114-118]) or three (Mandel 1989[88], Mandel 1992[89]) years of follow-up, patients in the TT group had AOM or OME 21% to 31% of the time, and patients in the WW group had AOM or OME 38% to 49% of the time. At later time points (age 6 and 9-11 years of age), Paradise[70,114-118] reported no longer any difference between groups in the percentage of patients presenting with either AOM or OME at a single follow-up visit: age 6 years (10.9% vs. 11.9%, p=0.77); age 9 to 11 years (6.2% vs. 5.1%; p=0.66) (Appendix Table G4).

OME recurrence

Rovers[67,139-141] (CoE III) (mean age 1.6 years at enrollment) found that the TT group had significantly less recurrent bilateral OME at all follow-up time points through 12 months, at which point 27% (TT) versus 53% (WW) of patients had bilateral OME (p<0.001). In addition, fewer patients in the TT group had bilateral OME at every follow-up visit through 12 months (3% vs. 27%) (p<0.001) (Appendix Table G5).

Balance and coordination

Balance and coordination were not reported by any of the seven trials that compared TT to WW.

Cholesteatoma

The Paradise[70,114-118] trial (CoE I) reported no cases of cholesteatoma in any tubed ears, and Mandel 1989[88] reported cholesteatoma in 0% (0/30) of TT patients and 3% (1/29) of WW patients, a difference which was not statistically significant. The one case of cholesteatoma was a floating piece of keratin in the middle ear which was removed by myringotomy and followed by TT insertion. Otherwise, cholesteatoma was not reported by any trial comparing TT to WW.

Functional and quality of life outcomes

Attention and behavioral outcomes

Two RCTs reported attention and behavioral outcomes: Paradise[70,114-118] (CoE I) (mean age 1.25 years at enrollment) and COMET[59,95,173] (CoE I) (mean age 2.9 years at enrollment). Results were somewhat conflicting, with one trial showing benefit at nine months but not at later time points, and the other trial showing differences between groups at any point through a mean of 72-130 months follow-up (Paradise[70,114-118]).

COMET[59,95,173] reported that at nine months, fewer patients in the TT group (30%) were considered to be at risk for behavioral problems than those in the WW group (47%) at nine months (RD -17%, 95% CI -33% to -1.7% (p=0.0311)) in one trial (COMET[59,95,173]) (Appendix Table G6). (Those at risk for behavioral problems scored 10 or higher on the Richman Behavior Checklist). The difference was no longer

meaningful by 18 months (24% versus 20%, RD 4%, 95% CI –10% to 19%, p=0.5733). COMET[59,95,173] also evaluated behavior at age 7 using the Strengths and Difficulties Questionnaire, which evaluates behavior, emotions, and relationships with peers. The questionnaire was teacher-reported, and no differences were found between TT and WW groups for any subscale (prosocial, hyperactivity, emotional problems, conduct problems, and peer problems) or total score.

Paradise[70,114-118] evaluated attention and behavioral outcomes using a number of different outcome measures at ages 3, 4, 6, and 9 to 11 years of age. These outcome measures were completed by both parents and teachers separately. At age 9 to 11 years, the mean parent-reported Child Behavior Checklist score was significantly worse (higher scores are less favorable) in the TT group (51 ± 12) than the WW group (48 ± 11) (MD 3.0, 95% CI 0.7 to 5.3, p=0.0107) but the difference for the same outcome measure when teacher-reported did not reach statistical significance (52 ± 11 (TT) vs. 50 ± 11 (WW), MD 2.0, 95% CI -0.2 to 4.2, p=0.0772). The clinical relevance of small differences in scores with overlapping standard deviations is questionable. Otherwise, there were no statistically meaningful differences between the TT (n=216) and WW (n=213) groups at any time point (Appendix Table H). Outcome measures evaluated include:

- Child Behavior Checklist: assesses overall behavioral and emotional health using a number of specific subscales (anxious/depressed, withdrawn, sleep problems, somatic problems, aggressive behavior, destructive behavior, social problems, thought problems, attention problems, and total problems; outcomes were reported at ages 3, 4, 6, and 9-11 years. The normative mean z-score is 50 ± 10, higher scores are less favorable.
- Children's Disruptive Behavior Disorders Rating Scale: assesses attention deficit-hyperactivity disorder, oppositional defiant disorder, and conduct disorders; outcomes were reported at age 9-11 years
- Impairment Rating Scales: evaluates relationships with others, the effect of any problems on the family, classroom behavior, academic functioning, self-esteem, and overall functioning; outcomes were reported for age 9-11 years
- Social Skills Rating System: assesses cooperation, assertion, self-control, and responsibility
- Continuous Performance Test: measures inattention and impulsivity in both audio and visual tests; outcomes were reported for age 9-11 years

Academic achievement

Two RCTs reported outcomes on academic achievement: Paradise[70,114-118] (CoE I) (mean age 1.25 years at enrollment) and COMET[59,95,173] (CoE I) (mean age 2.9 years at enrollment). The COMET[59,95,173] trial reported that at age 4.5 years (corresponding to approximately 0 to 40 months follow-up), school entry tests showed significantly better language (adjusted OR 3.45, 95% CI 1.42 to 8.39, p=0.006) and writing scores (adjusted OR 3.74, 95% CI, 1.51 to 9.27, p=0.004) in the TT versus WW groups. These differences were found only after adjusting for baseline variables (age, gender, maternal education, housing, and mother's parity). There were no differences between groups in the adjusted reading or math score. The same trial found that at age 7 to 8 years, there were no differences between groups in the SATS Key Stage 1 reading, writing, and math unadjusted or adjusted scores. Another trial (Paradise[70,114-118]) reported that at age 9 to 11, there were no differences between groups in any test evaluated, including the Woodcock-Johnson Achievement tests (math, spelling, and writing), Woodcock Reading Mastery Tests, or Oral Reading Fluency Test. Detailed results are available in Appendix Table G7.

Auditory processing

Four RCTs reported auditory processing: the MRC 2004 subset of the TARGET trial[99] (CoE II), Paradise[70,114-118] (CoE I), Mandel 1989[88] (CoE III), and Mandel 1992[89] (CoE III). This outcome was reported

in two different ways: as the noise threshold for speech recognition in two trials, and by using hearing-in-noise tests in two trials (Appendix Table G8).

In two trials that enrolled children aged 0.6 to 12 years, the noise threshold for speech recognition was lower in the TT group (range, 6.2 to 12.5 dB) compared with the WW group (range, 14.1 to 19.9 dB) at one, two, and four months follow-up, although the statistical significance of this result was not reported (and could not be calculated) (Mandel 1989[88], Mandel 1992[89])

The ability to understand speech in noise was evaluated by three different outcome measures. The MRC 2004 subset of the TARGET trial[99] used the speech-in-noise McCormick automated toy test, which measures the sound level required for the child to correctly identify the word given through headphones against background of 60 dB sound pressure level (SPL) pink noise. When measured as change from baseline (to control for baseline differences between groups in this outcome measure), patients in the TT group had improved significantly more than the WW group at three months (change from baseline: -6.1 versus -3.0 dB, p=0.003). However, there was no longer a difference between groups in mean improvement from baseline to 12 months (-5.0 versus -5.1 dB). Paradise[70,114-118] reported similar outcomes in both groups at age 6 (i.e., approximately 36 to 70 months follow-up) in the SCAN Screening Test for Auditory Processing Disorders, which evaluates auditory processing in terms of the ability to understand: two different words spoken at the same time in opposite ears, distorted words, and speech with background noise. Paradise[70,114-118] also employed the children's version of the Hearing in Noise test, which tests the loudness required in order for a child to be able to repeat a sentence spoken in a background of competing noise. The trial found no differences between TT and WW groups at age 9 to 11 (i.e., approximately 72 to 130 months follow-up).

Subanalysis: hearing levels in patients stratified by the presence of middle ear effusion
The two Mandel RCTs also found that speech-recognition thresholds measured at any point through three years follow-up were lower in both TT and WW groups in patients with either a functional tube or without middle ear effusion (in patients without an intact tube) (range across TT and WW groups, 4.5 to 8.5 dB) compared with those in which middle ear effusion was present (range across TT and WW groups, 18.7 to 20.4 dB) ($p<0.001$ for both studies) (Mandel 1989[88], Mandel 1992[89]). The differences between the TT and WW groups were small, ranging from 0.5 to 2.7 dB lower in the TT group.

Speech and Language Development
Four RCTs reported speech and language outcomes: COMET[59,95,173] (CoE I), Rovers[67,139-141] (CoE III), Paradise[70,114-118] (CoE I), and Rach[127,177] (CoE III). Overall, there were no differences between groups at any time point.

Outcomes could be pooled from three trials that enrolled patients aged 1.2 to 4.7 years. Between six and nine months follow-up, there was no difference between TT and WW groups in verbal comprehension scores using the Reynell test (pooled standardized mean difference 0.09 (95% CI -0.21 to 0.39, p=0.55), Figure 5), although statistical heterogeneity was moderate (I^2=49%). Pooled results were also similar between groups for expressive language scores using either the Reynell test (COMET[59,95,173], Rach[127,177]) or the Schlichting test (Rovers[67,139-141]) (pooled mean difference, 0.03 (95% CI -0.42 to 0.49), p=0.90), Figure 6), however heterogeneity between studies was substantial (I^2=79%).

Figure 5. Verbal comprehension (Reynell test) at 6 to 9 months: TT vs. WW for OME

Study	TT Mean	TT SD	TT Total	WW Mean	WW SD	WW Total	Weight	Std. Mean Difference IV, Random, 95% CI
Rovers (6 months)	−0.06	0.95	93	0.06	1.05	94	42.0%	−0.12 [−0.41, 0.17]
Rach (6 months)	0.17	0.61	22	0.11	0.55	21	18.3%	0.10 [−0.50, 0.70]
COMET (9 months)	−0.04	1.02	87	−0.35	0.98	77	39.6%	0.31 [−0.00, 0.62]
Total (95% CI)			**202**			**192**	**100.0%**	**0.09 [−0.21, 0.39]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.96$, df = 2 (P = 0.14); $I^2 = 49\%$
Test for overall effect: Z = 0.59 (P = 0.55)

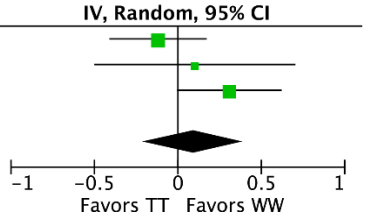
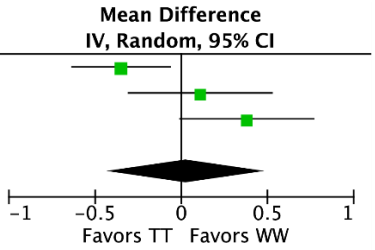


Figure 6. Expressive language (Reynell or Schlichting test) at 6 to 9 months: TT vs. WW for OME

Study or Subgroup	TT Mean	TT SD	TT Total	WW Mean	WW SD	WW Total	Weight	Mean Difference IV, Random, 95% CI
Rovers (6 months)	−0.18	1.19	93	0.17	0.74	94	36.3%	−0.35 [−0.63, −0.07]
Rach (6 months)	0.29	0.75	22	0.18	0.64	21	31.3%	0.11 [−0.31, 0.53]
COMET (9 months)	−0.62	1.27	87	−1	1.25	76	32.4%	0.38 [−0.01, 0.77]
Total (95% CI)			**202**			**191**	**100.0%**	**0.03 [−0.42, 0.49]**

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 9.57$, df = 2 (P = 0.008); $I^2 = 79\%$
Test for overall effect: Z = 0.13 (P = 0.90)



At 12 to 18 months, results were similar between groups after controlling for differences in baseline variables (results could not be pooled because standard deviations were not reported). For the Reynell test verbal comprehension, the Rovers[67,139-141] trial reported that the TT group had improved 0.7 month more than the WW group by 12 months (95% CI, -0.3 to 1.7, p=0.18); the COMET[59,95,173] trial reported a mean difference in standard scores at 18 months that was 0.17 higher in the TT group (95% CI, -0.21 to 0.56, p=0.37). For the Reynell test expressive language, the adjusted mean difference was 0.14 higher in the TT group (95% CI, -0.28 to 0.56, p=0.51) as reported by the COMET[59,95,173] trial. Results are also presented in Appendix Table G9.

The COMET[59,95,173] trial also reported that at age 7 to 8 (~28 to 82 months follow-up), there was no difference between groups in measures of comprehension, oral expression, and non-word repetition. The Paradise[70,114-118] trial (mean age 1.25 years at enrollment) reported that overall, there was no difference between TT and WW groups in a variety of different measures of language development (receptive language, expressive language, and phonological memory) at age 3 (~0 to 34 months follow-up), 4 (~12 to 46 months follow-up), 6 (~36 to 70 months follow-up), and 9 to 11 (~72 to 130 months follow-up). Detailed results are available in Appendix Table G10.

Parent satisfaction with treatment/outcomes

None of the included studies reported this outcome.

Patient quality of life and parent quality of life

Two trials evaluated quality of life: Rovers[67,139-141] (CoE III) (mean age 1.6 years at enrollment) and Paradise[70,114-118] (CoE I) (mean age 1.25 at enrollment). Overall, there were no differences between groups in patient quality of life or in parent-child interaction. No trials directly evaluated parent quality of life.

Patient quality of life was evaluated directly in only one trial using the TAIQOL (TNO-AZL Infant Quality of Life) outcome measure (Rovers[67,139-141]). This trial found no significant differences at 6 or 12 months

follow-up in any subdomain of the TAIQOL, including vitality, appetite, communication, motoric, social, anxiety, aggression, eating, and sleeping domains (see Appendix Table G11 for details).

Both trials reported measures of parent-child interaction, which may be considered aspects of both patient and parent quality of life. Rovers[67,139-141] reported similar outcomes between groups at 6 and 12 months in all subdomains of the Erikson Child-Parent Interaction test, including parent hostility, parent structure, parent respect, parent supportive, parent quality, child affection, child avoidance, child compliance, child negativism, and child reliance. Paradise[70,114-118] found no differences between groups in any subdomain of the Parenting Stress Index (in which parents grade the parent-child relationship) at age 3 (~0 to 34 months follow-up), 4 (~12 to 46 months follow-up), and 6 (~36 to 70 months follow-up). Subdomains of the Parenting Stress Index included parental distress, parent-child dysfunctional interaction, difficult child, and total stress. Detailed results are available in Appendix Table G12.

Pain

One trial reported pain outcomes: Rovers[67,139-141] (CoE III). This trial, which enrolled infants, found no difference between TT and WW groups at any time point evaluated through 12 months in the incidence of parent-reported earache, with earache occurring in 2.4% to 9.9% fewer TT versus WW patients ($p \geq 0.1097$). Similarly, there were no differences between groups in the incidence of parent-reported fever ($p \geq 0.1199$). See Appendix Table G13 for additional details.

Patient satisfaction with treatment/outcomes

None of the included studies reported this outcome.

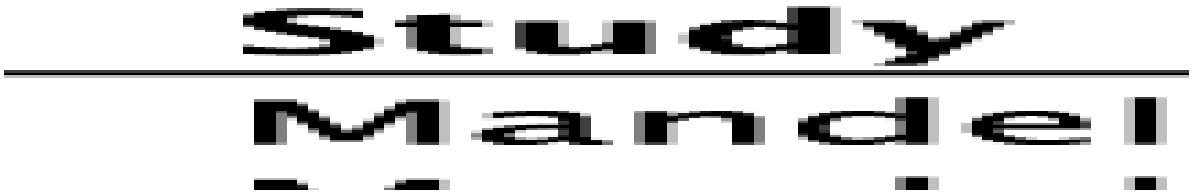
Healthcare utilization

Surgery

Tube reinsertion in the TT group or tube placement in the WW group was reported by six trials: Paradise[70,114-118] (CoE I), COMET[59,95,173] (CoE I), TARGET[98,100] (CoE II), Rovers[67,139-141] (CoE III), Mandel 1989[88] (CoE III), and Mandel 1992[89] (CoE III). Overall, the results suggest that in the first year, TT patients are less likely to undergo surgery (reinsertion) than WW patients (initial tube placement). Cumulative results from baseline through 18-24 months suggest the same effect. However, there was no difference in tube placement between groups in the second year of follow-up (i.e., 12-24 months), with 15.8% of TT patients undergoing tube placement versus 19.2% in the WW group across three trials, or in the third year of follow-up (i.e., 24-36 months) based on two small trials. Data are available in table format in Appendix Table 14.

In the first 12 months of follow-up pooled and individual results from three trials (TARGET[98,100], Mandel 1989[88], Mandel 1992[89]) suggested that the TT group was significantly less likely to undergo tube placement than the WW group (pooled RD -42%, 95% CI -50% to -35%, $p<0.00001$, $I^2=0\%$) (Figure 7) based on data from 368 patients across the three trials, only 4.8% of patients underwent reinsertion while 47.0% of patients underwent tube placement. In the first 18 months, a fourth trial (COMET[59,95,173]) similarly found that patients in the TT group were significantly less likely to undergo surgery (19% versus 88%, RD -69%, 95% CI -79% to -58%, $p<0.001$). In the first 24 months, the TARGET[98,100] trial reported that 12.7% of TT patients and 56.6% of WW patients underwent surgery, a difference that was statistically meaningful (RD -43.9%, 95% CI -54.4% to -33.3%, $p<0.001$).

Figure 7. Surgery (tube placement) through 12 months: TT vs. WW for OME



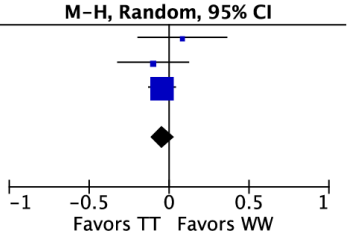
*TARGET: Tubes ± adenoidectomy ± tonsillectomy

Between 12 and 24 months, data across the same three trials (N=354) suggest no difference between TT and WW groups (15.8% versus 19.2%, pooled RD -4%, 95% CI -12% to 3%, p=0.27, I^2=0%) (Figure 8), and there was no difference between TT and WW groups in surgery performed between 24 and 36 months (pooled RD -10%, 95% CI -14% to 12%, p=0.89, I^2=0%) in two trials with a total of 98 patients (Mandel 1989[88], Mandel 1992[89]) (Figure 9). Overall, reported that TT patients were 36% less likely to undergo tube reinsertion than WW patients were to undergo tube insertion (35% versus 71%, RD -36%, 95% CI -58% to -15%, p=0.0022).

Figure 8. Surgery (tube placement) between 12 and 24 months: TT vs. WW for OME

	TT		WW			Risk Difference	Risk Difference
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Mandel 1989	9	27	4	16	7.2%	0.08 [-0.19, 0.36]	
Mandel 1992	7	30	11	33	11.3%	-0.10 [-0.32, 0.12]	
TARGET*	13	126	18	122	81.5%	-0.04 [-0.13, 0.04]	
Total (95% CI)		**183**		**171**	**100.0%**	**-0.04 [-0.12, 0.03]**	
Total events	29		33				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.06, df = 2 (P = 0.59); I^2 = 0%
Test for overall effect: Z = 1.09 (P = 0.27)

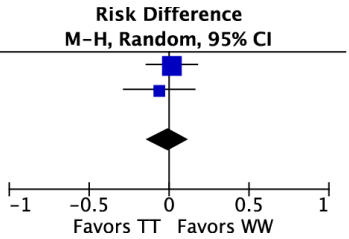


*TARGET: Tubes ± adenoidectomy ± tonsillectomy

Figure 9. Surgery (tube placement) between 24 and 36 months: TT vs. WW for OME

	TT		WW			Risk Difference	Risk Difference
Study	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Mandel 1989	2	25	1	16	66.1%	0.02 [-0.14, 0.18]	
Mandel 1992	6	28	8	29	33.9%	-0.06 [-0.28, 0.16]	
Total (95% CI)		**53**		**45**	**100.0%**	**-0.01 [-0.14, 0.12]**	
Total events	8		9				

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.41, df = 1 (P = 0.52); I^2 = 0%
Test for overall effect: Z = 0.14 (P = 0.89)



The other two trials did not report comparative data. Paradise[70,114-118] did not report on reinsertions in the TT group; in the WW group (n=196) tubes were placed in the following percentage of patients: 2.0% (≤1 month), 4.6% (≤2 months), 11.2% (≤6 months), 33.2% (age 3 (~0-34 months)), 38.3% (age 4 (~12-46 months)), 40.3% (age 6 (~36-70 months)), and 45.0% (age 9-11 (~72-130 months)). Rovers[67,139-141] reported that through six months, 9% of patients in the TT group underwent reinsertion, while through 12 months, 10.6% of WW patients underwent tube placement.

Medication usage

One trial of infants evaluated the use of antibiotics: Rovers[67,139-141] (CoE III). Antibiotic ear drops were prescribed to significantly more patients in the TT group (62%) as compared to the WW group (10%), a risk difference of 52% (95% CI 40% to 63%, p<0.001) (Appendix Table G15). Similar results were found for the subset of patients prescribed two or more course of antibiotic ear drops (41% versus 4%, RD 37%, 95% CI 26% to 47%, p<0.001). Oral antibiotics were prescribed to more TT than WW children, although the results did not reach statistical significance (34% versus 22%, 95% CI -1% to 25%, p=0.0678). The authors correlated these findings with the fact that that significantly more TT patients developed otorrhea through 12 months than did WW patients (83% versus 38%, RD 45%, 95% CI 32% to 57%, p<0.001), although the cause and effect of this correlation was not established.

Number of office visits

None of the included studies reported this outcome.

4.1.3. OME: Tube (one ear) versus No surgery (opposite ear) (by-ear analysis)

Studies included

Five RCTs reported across eight publications[14,38,83,90-94] were identified for inclusion. Note that based on study dates, patient numbers and characteristics, it is possible that patients in one trial (Maw 1991[90]) overlap partially or completely with those reported in another (Maw and Bawden 1993/1994[91-94]) however, because insufficient detail was reported to definitively indicate that these were patients from the same trial, they were treated here as separate trials. No cohort studies met the inclusion criteria. For this comparison, studies which compared tympanostomy tube (TT) insertion in one ear to no treatment in the contralateral ear were sought. By design, this comparison is only applicable to studies that performed by-ear analysis (rather than by-child analysis), and all children underwent surgery.

Study characteristics

The included trials were published between the years 1983 to 1994 and allocated between 35 and 185 patients to this comparison. All patients were randomized by ear to receive a TT in one ear and no treatment in the other ear; all patients underwent surgery. Mean patient age ranged from 3.9 to 6.0 years across three trials (Black[14], Dempster[38], Lildholdt[83]); two trials (Maw and Bawden[91-94], Maw 1991[90]) reported only that patients ranged in age from 2-3 to 9 years. Across the trials, 34% to 56% of patients were females. All trials included only patients with bilateral OME; two required OME duration to be three months or longer (Dempster[38], Maw and Bawden[91-94]) and the other three trials did not require a specific OME duration. Hearing loss was required in two trials (Dempster[38], Maw and Bawden[91-94]); two other trials did not require hearing loss but mean baseline hearing levels suggested that overall patients had hearing loss. No trials required any additional symptoms for inclusion. Study characteristics, including quality assessment ratings, are summarized in Table 9.

Intervention details are summarized in Table 10. Briefly, patients underwent surgery with general anesthesia. Some trials did not specify the use of general anesthesia, however, there was no indication otherwise. Patients received a tube in one ear and did not have any treatment in the contralateral ear. One trial (Lildholdt[83]) noted that 35% of patients underwent simultaneous tonsillectomy but no other details were reported; the study did not stratify results based on the addition of this procedure. Tube reinsertion was required in two trials (Maw and Bawden[91-94], Maw 1991[90]) if there was fluid in ear after tube extrusion and fluid still present in the unoperated ear when there was subjective and objective hearing loss; this requirement led to a higher rates of tube reinsertion than the other studies (see Table

8B for details). Tube reinsertion was permitted in another trial (Lildholdt[83]) avoided if at all possible in one trial (Black[14]), and not permitted in one trial (Dempster[38]) (see Table 10 for details).

Table 9. Study characteristics and patient demographics: Unilateral TT vs. contralateral no surgery for OME

Study	N	Interventions (n)	OME	Hearing loss	Additional symptoms required	Age range (mean)	Female (%)	Special pop.	F/U time points (%)	Study quality
RCTs										
Black 1990[14]	149	• Unilateral TT, contralateral no treatment, (n=37) • (Unilateral TT, contralateral myringotomy, n=37) • (Ad + unilateral TT, contralateral myringotomy n=37) • (Ad + unilateral TT, contralateral no treatment n=38)	Bilateral (duration NR)	Not required (mean hearing level at baseline: 27.5 dB)	-	4 – 9 yrs. (6.0 yrs.)	35%	-	1.75 mos. (% NR) 6 mos. (% NR) 12 mos. (85%) 24 mos. (61%)	CoE II
Dempster 1993[38]	78	• Unilateral TT, contralateral no treatment (n=35*) • (Ad + unilateral TT, contralateral no treatment, n=37*)	Bilateral (≥3 months)	Hearing loss required (≥25 dB) for ≥3 mos.	-	4 – 9 yrs. (5.7 yrs.)	34%	-	6 mos. (92%) 12 mos. (92%)	CoE III
Lildholdt 1983[83]	150	• Unilateral TT† (150	Bilateral (duration NR)	Not required (mean 23 ± 11	-	1 – 10 yrs. (3.9 yrs.)	43%	-	Mean 38 mos. (89.3%)	CoE III

Study	N	Interventions (n)	OME	Hearing loss	Additional symptoms required	Age range (mean)	Female (%)	Special pop.	F/U time points (%)	Study quality
		ears) • Unilateral no treatment† (150 ears)		dB at baseline in both ears)						
Maw and Bawden 1993, 1994 (4 papers)[91-94]	228	• Unilateral TT, contralateral no treatment (n=87) • (Ad or Ad/Tons + unilateral TT, contralateral no treatment, n=141)	Bilateral (≥3 months)	Hearing loss required (≥25 dB for ≥3 months)	-	2 – 9 yrs. (mean NR)	42%*	-	6 mos. (82%) 12 mos. (90%) 24 mos. (80%) 36 mos. (66%) 48 mos. (59%) 60 mos. (52%) 84 mos. (38%) 120 mos. (17%)	CoE II
Maw 1991[90]	185‡	• Unilateral TT (185 ears) • Unilateral no treatment (185 ears)	Bilateral (duration NR)	NR	-	3 – 9 yrs. (mean NR)	40%	-	1.5, 4, 6, 9, 12, 15, 18, 24, 36, 48, 60 mos. (% NR)	CoE III
Cohort Studies										
(none)										

F/U: follow-up; NR: not reported; pop.: population

*Data reported only for those with complete follow-up

†Lildholdt 1983: Tonsillectomy performed in 35% of patients; results not stratified according to tonsillectomy.

‡Maw 1991: the 185 patients in this study may overlap (completely or partially) with patients in the Maw and Bawden trial; however, insufficient detail was reported to make a definitive conclusion.

Table 10. Intervention details: Unilateral TT versus contralateral no treatment for OME

Study	Interventions (n)	Treatment Protocol	Indication for Tube (Re)insertion	Tube (Re)insertion (%)
RCTs				
Black 1990[14]	TT (37 ears)	• Anesthesia NR • Unilateral • Tube type NR	• At discretion of treating otolaryngologist, who were asked by investigators to avoid surgical treatment whenever possible	• NR
	No treatment (37 ears)	• General anesthesia • Unilateral	• same	• NR
Dempster 1993[38]	TT (35 ears)	• General anesthesia • Unilateral • Shah tube	• Not permitted	• 0%
	No treatment (35 ears)	• General anesthesia • Unilateral	• Not permitted	• 0%
Lildholdt 1983[83]	TT (150 ears)	• General anesthesia • Unilateral • Donaldson tube • Tonsillectomy: 35% patients (results not stratified by this procedure)	• Recurrent OME with flat tympanogram for ≥3 mos., and fluid found upon myringotomy	• Mean 38 months: 17% ears
	No treatment (150 ears)	• General anesthesia • Unilateral • Tonsillectomy: 35% patients (results not stratified by this procedure)	• No specific criteria were followed • The 8% no treatment ears that received tubes had hearing loss in TT ear that could not be corrected and suspected delay in language development	• Mean 38 months: 8% ears
Maw and Bawden[91-94]	TT (87 ears)	• General anesthesia	• Reinsertion required if there	• ≤12 months: 37%

Study	Interventions (n)	Treatment Protocol	Indication for Tube (Re)insertion	Tube (Re)insertion (%)
		• Unilateral • Shepard or Goode tube	was fluid in ear after tube extrusion and fluid still present in the unoperated ear when there was subjective and objective hearing loss	• ≤24 months: ~64% • ≤36 months: ~66% • ≤48 months: ~66% • ≤60 months: 68%
	No treatment (87 ears)	• General anesthesia • Unilateral	• NR	• NR
Maw 1991*[90]	TT (185 ears)	• Anesthesia NR • Unilateral • Tube type NR	• Reinsertion required if there was fluid in ear after tube extrusion and fluid still present in the unoperated ear when there was subjective and objective hearing loss	• ≤60 months: 49%
	No treatment (185 ears)	• Anesthesia NR • Unilateral	• NR	• NR

F/U: follow-up; NR: not reported; pop.: population

*Maw 1991: the 185 patients in this study may overlap (completely or partially) with patients in the Maw and Bawden trial; however, insufficient detail was reported to make a definitive conclusion

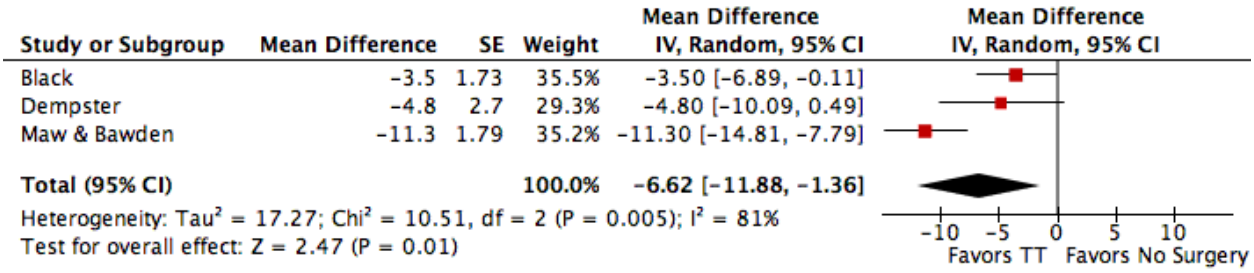
Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G16-G17).

Clinical outcomes

Hearing levels
Four trials reported hearing levels by ear: Black[14] (CoE II) (mean age 6.0 years at enrollment), Dempster[38] (CoE III) (mean age 5.7 years at enrollment), Lildholdt[83] (for the subset of patients aged 5 to 10 years only) (CoE III), and Maw and Bawden[91-94] (CoE II) (age range 2 to 9 years at enrollment). While only two trials required hearing loss (hearing level ≥25 dB) for inclusion (Dempster[38] and Maw and Bawden[91-94]), baseline hearing levels (range of means: 23-27.5 dB) in the other two trials (Black[14], Lildholdt[83]) suggested that the majority of patients had hearing loss at study entry. Data are presented in table format in Appendix Table G16. Overall results suggest that there is a modest benefit with TT at 6 months, but by 12 months there was no difference between groups. Note that results reported at 36 months and later are subject to bias due to follow-up of less than 80% of patients.

At six months, pooled results from three trials (Maw and Bawden[91-94], Dempster[38], Black[14]) suggest that hearing levels as measured by audiography were significantly better in the TT ear compared with the no treatment ear, with a pooled mean difference of -6.6 dB (95% CI -14.8 to -7.8 dB, p=0.01) (Figure 10). The pooled estimate has considerable statistical heterogeneity (I_2=81%), however, likely stemming from the different estimate provided from the Maw and Bawden trial. Data from one other trial (Lildholdt[83]) could not be pooled (means and standard deviations were not reported) but suggested that there was no statistical difference between groups in mean hearing levels at 6 months (~12 dB for TT versus ~14 dB for no treatment). Overall, results from three studies suggest a modest benefit (2-5 dB) with TT, while a fourth study suggests a larger benefit (11 dB) with TT at six months. One of these trials (Dempster[38]) also reported air bone gap hearing levels and similarly found a slight benefit hearing levels at six months with TT versus no treatment (17.3 ± 11.3 vs. 22.6 ± 11.0, MD -5.3, 95% CI -10.6 to 0.02, p=0.0508).

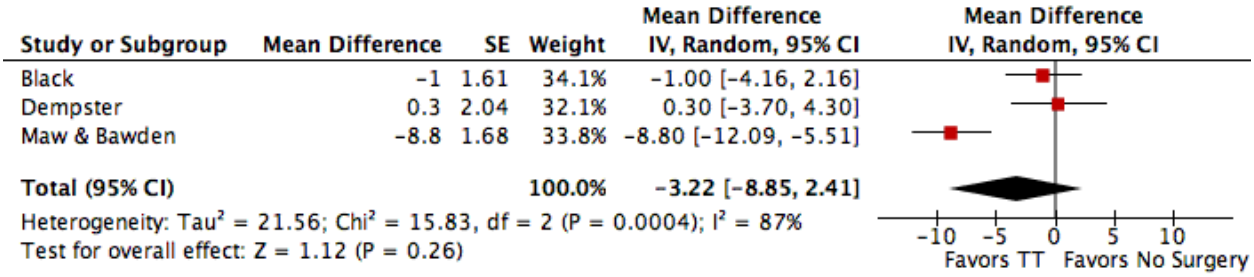
Figure 10. Hearing levels by ear at 6 months: TT (unilateral) vs. no treatment (contralateral) for OME



By 12 months, pooled results from the same three trials (Maw and Bawden[91-94], Dempster[38], Black[14]) suggested no statistical difference between ears in mean audiometric hearing levels (pooled MD -3.2 dB, -8.9 to 2.4 dB, p=0.26) (Figure 11). Again, statistical heterogeneity between trials was considerable (I^2=87%) and likely stems from the considerably different estimate provided by the Maw and Bawden[91-94] RCT. In this trial, tube reinsertion had been performed in 37% of TT ears (and presumably in no control ears) by 12 months, which may have helped to sustain the hearing benefit from tubes. In contrast, tube reinsertion did not occur in the other two trials (Black[14], Dempster[38]). Unpoolable data from the Lildholdt[83] trial similarly found difference between groups in mean hearing levels at 12 months (~12 dB

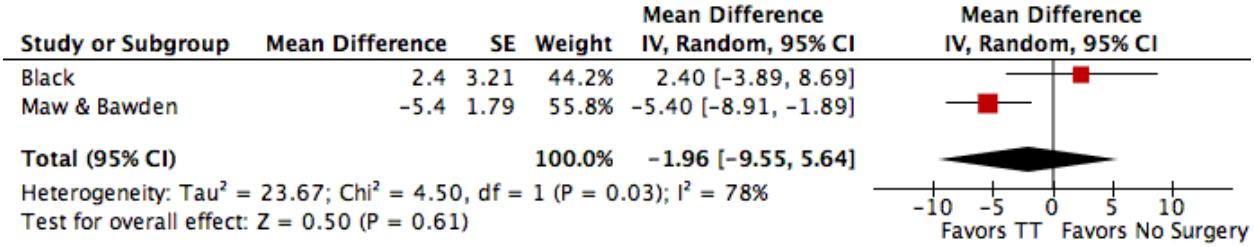
for both groups). Overall, results from three studies suggest no benefit (-0.3 to 1 dB) with TT, while a fourth study suggests a larger benefit (9 dB) with TT at twelve months. The Dempster[38] also reported similar air bone gap hearing levels between groups at 12 months (17.9 ± 9.9 vs. 17.2 ± 10.0).

Figure 11. Hearing levels by ear at 12 months: TT (unilateral) vs. no treatment (contralateral) for OME



At 24 months, there was no difference in hearing levels between ears based on the pooled estimate from two trials (Maw and Bawden[91-94], Black[14]) (Figure 12). Again, the estimates of effect are different between the two studies, with the Maw and Bawden[91-94] suggesting significantly better hearing in the TT ear and the Black[14] study showing no difference between groups. The high percentage of TT ears in the Maw and Bawden trial (~64% through 24 months) likely help to sustain the hearing improvement seen with tubes, while TT ears in the Black trial presumably did not undergo reinsertion. Unpoolable data from the Lildholdt[83] trial similarly found difference between groups in mean hearing levels at 24 months (~13 dB for both groups).

Figure 12. Hearing levels by ear at 24 months: TT (unilateral) vs. no treatment (contralateral) for OME



At 36 months, two trials reported hearing levels measured by audiography. Maw and Bawden[91-94] (n=87 patients) reported that the TT ears still had marginally better hearing levels than the ears randomized to no treatment (19.8 ± 9.4 for 57 ears vs. 23.5 ± 10.5 dB for 65 ears, respectively), with a mean difference of -3.7 (95% CI, -7.3 to -0.1) dB (p=0.0437). The sustained improvement in the TT group may be due in part to the fact that approximately 66% of TT ears had undergone tube reinsertion; this data was not reported for the no treatment ear. In contrast, Lildholdt[83] reported hearing levels of approximately 13 dB in both ears (N=48) at 36 months; this trial reported that 17% of TT and 8% of no treatment ears had undergone tube (re)insertion through a mean of 38 months.

By 48 months, two trials reported no difference in mean hearing levels between ears; hearing was measured by audiography. Maw and Bawden[91-94] reported mean hearing thresholds of 18.7 ± 7.3 dB in the TT ears (n=57) and 20.0 ± 8.8 in the no treatment ears (n=65) (mean difference -1.3, 95% CI -4.3 to 1.7 dB), and Lildholdt[83] reported hearing levels of about 10 dB in both ears (N=24).

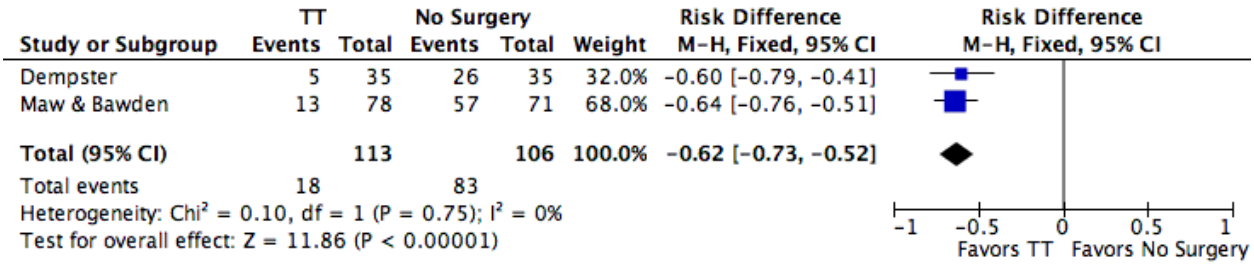
One trial (Maw and Bawden[91-94]) reported no significant difference between ears at 60 months (17.6 ± 7.0 (47 ears) vs. 19.4 ± 8.6 (56 ears)), 84 months (15.6 ± 6.2 (35 ears) vs. 17.9 ± 9.0 (43 ears)), or 120 months (15.5 ± 7.1 (15 ears) vs. 16.6 ± 8.8 (20 ears)).

OME recurrence

Three trials reported OME recurrence by ear: Dempster[38] (CoE III) (mean age 5.7 years at enrollment), Lildholdt[83] (for the subset of patients aged 5 to 10 years only) (CoE III), and Maw and Bawden[91-94] (CoE II) (age range 2 to 9 years at enrollment). Data are presented in table format in Appendix Table G17. Results reported at 36 months and later are subject to bias due to follow-up of less than 80% of patients.

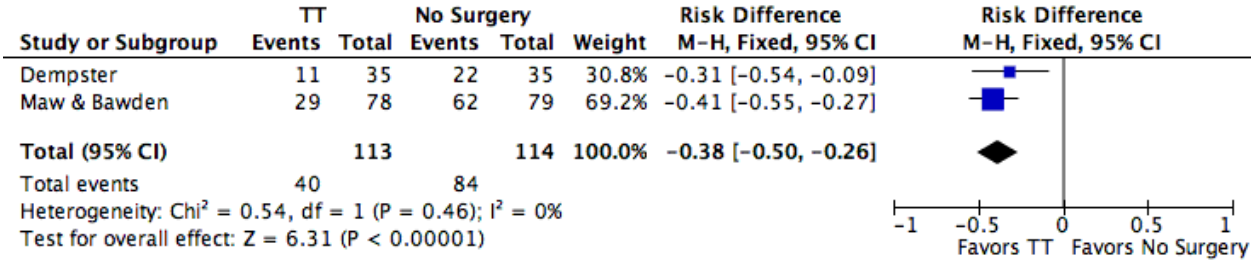
At six months, pooled data from two small trials (Dempster[38], Maw and Bawden[91-94]) suggested that OME (as detected by otoscopy) was present in 62% fewer ears randomized to TT compared with those randomized to no treatment: pooled RD -62%, 95% CI -73% to -52%, p<0.00001, I^2=0% (Figure 13). Similar results were found in one trial (Dempster[38]) for OME as detected by tympanometry at six months (34% of TT versus 79% of no treatment ears, RD -46%, 95% CI -66% to -25%, p=0.001) (Appendix Table .

Figure 13. OME recurrence by ear at 6 months: TT (unilateral) vs. no treatment (contralateral) for OME



The same two small trials reported that more TT ears had OME as detected by otoscopy at 12 months than was seen 6 months, although the pooled mean difference between the TT and no treatment ears remained statistically meaningful: RD -38%, 95% CI -50% to -26%, p<0.00001, I^2=0% (Figure 14). At the same time point, one trial (Dempster[38]) reported that fewer TT ears had OME as detected by tympanometry than no treatment ears, although the results did not reach statistical significance due to small sample size (N=35) (46% of TT versus 68% of no treatment ears, RD -23%, 95% CI -45% to 0%, p=0.0551).

Figure 14. OME recurrence by ear at 12 months: TT (unilateral) vs. no treatment (contralateral) for **OME**



One trial of 87 patients reported that OME occurred less commonly in the TT ear at 24 months (31% vs. 63%, RD -31%, 95% CI -47% to -15%, p=0.0002) based on data from 70 and 72 ears, respectively. Similar results were found at later time points, but the results are particularly subject to bias due to high loss to

follow-up: 36 months (35% vs. 41% (p=NS) based on data from 57 and 59 ears, respectively), 48 months (24% vs. 41% (p=0.0571) based on data from 51 and 59 ears, respectively), 60 months (7% vs. 31% (p=0.0027) based on data from 45 and 55 ears, respectively), 84 months (12% vs. 15% (p=NS) based on data from 33 and 40 ears, respectively), and 120 months (7% vs. 10% (p=NS) based on data from 15 and 21 ears, respectively).

Over a mean follow-up of 38 months, one trial (Lildholdt[83]) reported that TT and no treatment ears had a similar incidence of fluid in the ears at any check-up (41.3% versus 48.7% of ears, respectively, RD -7.3%, 95% CI -18.6% to 3.9%, p=0.2025); these data reflect the percentage of patients with a flat tympanogram at any visit over the entire study period. The authors reported that flat tympanograms were present at 1% to 20% of checkups in 14.0% versus 25.3% of ears, respectively; this difference was statistically meaningful (RD -11.3%, 95% CI -20.2% to -2.4%, p=0.0137). However, the percentage of patients with flat tympanograms was statistically similar between ears at 21% to 40% of checkups (16.7% vs. 15.3% of ears, respectively) and well as at 41% to 100% of checkups (10.6% versus 8.0% of ears, respectively).

Otorrhea

Lildholdt[83] (CoE III) (mean age 3.9 years at enrollment) reported chronic suppurative otitis in 29.9% of TT ears through 60 months; the condition was treated with aura toilet, antibiotics, and tube removal if necessary. No data were reported for the untreated ear.

AOM episodes, Cholesteatoma

None of the included studies reported any of these clinical outcomes.

Functional and quality of life outcomes

None of the included studies reported any functional or quality of life outcomes, including auditory processing, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, or pain. Other outcomes of interest (attention and behavioral outcomes, academic achievement, speech and language development, patient and parent quality of life) can only be evaluated by child and are not applicable to this comparator where each child received a tube in one ear and no treatment in the other ear.

Healthcare utilization

Surgery

Tube insertion (i.e., reinsertion in the TT ear and tube placement in the no treatment ear) was reported by three trials: Lildholdt[83] (CoE III) (mean age 3.9 years at enrollment), Maw and Bawden[91-94] (CoE II) (age range 2 to 9 years at enrollment), and Maw 1991[90] (CoE III) (age range 3 to 9 years at enrollment). Data are available in Table 10.

The Maw and Bawden[91-94] and Maw 1991[90] studies had relatively high reinsertion rates; this is likely due to the study requirements that reinsertion take place if there was fluid in the ear after tube extrusion in patients who had fluid in the unoperated ear and who had subjective and audiometric hearing loss. In the Maw and Bawden[91-94], 37% of patients underwent reinsertion during the first year, and by 24 months, approximately 64% of patients had undergone reinsertion. After 24 months, relatively few reinsertions were performed, with 68% of patients having gone a tube reinsertion in the TT ear by 60 months follow-up. Overall, patients had a mean of 2.4 ± 1.4 grommets inserted in the TT ear through 60

months. In the Maw 1991[90] trial, 49% of patients underwent tube reinsertion in the TT ear through 60 months. Neither study reported tube insertion in the ear randomized to no treatment.

Lildholdt[83] permitted tube reinsertion in the TT ear if there was OME with flat tympanogram for at least three months after extrusion and fluid found upon myringotomy; 17% of patients underwent tube reinsertion in the TT ear through a mean follow-up of 38 months. No specific criteria were followed to guide tube insertion in the ear randomized to no treatment; overall, 8% of no treatment ears received tubes during the same follow-up period. In all cases, tubes were placed in the no treatment ears when there was hearing loss in the TT ear that could not be corrected along with a suspected delay in language development.

Medication usage

One trial (Lildholdt[83]) reported that local antibiotics were used in ears with drainage (29.9%) and that steroid-antibiotic ointment was used for granulation tissue formation (4.0%), however results were not stratified according to tube placement versus no treatment.

Number of office visits

None of the included studies reported this outcome.

4.1.4. OME: Tubes versus Myringotomy

Studies included

Seven RCTs reported across eight publications[14,35,48,49,73,76,88,89] met the inclusion criteria. Of these, four trials randomized patients to either bilateral TT or myringotomy (D'Eredita 2006[35], Gates 1987/1989[48,49], Mandel 1989[88], Mandel 1992[89]), and three trials randomized children by ear to unilateral TT and contralateral myringotomy (Black 1990[14], Kent 1989[73], Koopman 2004[76]). No cohort studies met the inclusion criteria.

Study characteristics

The trials were published between 1987 and 2006. For the four trials that randomized to TT versus myringotomy by child, between 30 and 227 patients were allocated to these treatments; patients had either bilateral or unilateral OME (see Table 11 for details). For the three trials that randomized to unilateral TT versus contralateral myringotomy, between 30 and 227 patients with bilateral OME were allocated. Mean patient age ranged from 3.7 to 6.1 years across four trials (D'Eredita 2006[35], Black 1990[14], Kent 1989[73], Koopman 2004[76]); three trials did not report mean age and patients ranged in age from 4 to 8 years in one trial (Gates 1987/1989[48,49]) and from 0.6 to 12 years in two trials (Mandel 1989[88], Mandel 1992[89]). Females comprised 17% to 59% of patients.

One trial (Mandel 1989[88]) stratified patients at entry by the presence of significant hearing loss (n=23) or no significant hearing loss (n=57): for the subgroup with "significant" hearing loss, Mandel 1989[88] required baseline hearing levels greater than 20dB if bilateral or greater than 40 dB if unilateral, while Koopman 2004[76], which required hearing impairment (not defined) for at least three months. Two trials did not require hearing loss for inclusion but indicated baseline hearing levels consistent with hearing loss: Black 1990[14] reported a mean baseline hearing level of 28.4 dB, and Kent 1989[73] reported that 80% of patients had "deafness" (not defined) at baseline. Two trials required that patients have hearing loss that did not exceed prespecified thresholds: for the subgroup with "no significant" hearing loss, Mandel 1989[88] required baseline hearing levels no higher than 20 dB if bilateral or no higher than 40 dB if

unilateral; Mandel 1992[89] required baseline hearing levels no higher than 35 dB. Neither study reported mean baseline hearing levels. Two studies did not require baseline hearing loss and did not report baseline hearing levels (D'Eredita 2006[35], Gates 1987/1989[48,49]). No trials required any additional symptoms for inclusion. Study characteristics, including quality assessment ratings, are summarized in Table 11.

Intervention details are summarized in Table 12. Patients received TT or myringotomy under general anesthesia; while two trials did not specify the use of general anesthesia, there was no indication otherwise. In the trials randomized by patient, tubes were placed bilaterally in two trials (D'Eredita 2006[35], Gates 1987/1989[48,49]) and either unilaterally (range, 13-41% of patients) or bilaterally (range, 59-87% of patients) in two trials (Mandel 1989[88], Mandel 1992[89]). In the trials randomized by ear, TT was placed unilaterally and myringotomy done in the contralateral ear (Black 1990[14], Kent 1989[73], Koopman 2004[76]). The method by which myringotomy was performed and time to healing of the opening varied: one trial (D'Eredita 2006[35]) employed contact-diode laser myringotomy, the opening healed within 3.5 months. Another used laser myringotomy (Koopman 2004[76]) and indicated that the opening healed within two months; one trial used thermal myringotomy (Kent 1989[73]) and noted that the opening healed on average after 0.5 months (range, 0.2 to 1.5 months). Two trials indicated that myringotomy was done by creating a wide circumferential incision (Mandel 1989[88], Mandel 1992[89]), and two trials did not report any details on the procedure (Gates 1987/1989[48,49], Black 1990[14]); none of these four trials reported time to healing of the incision. Details on when tube (re)insertion was permitted were provided by four trials (see Table 12 for details); the other three trials did not provide information regarding tube reinsertion (D'Eredita 2006[35], Kent 1989[73], Koopman 2004[76]).

Table 11. Study characteristics and patient demographics: TT vs. Myringotomy for OME

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
TT versus Myringotomy: randomized by patient										
D'Eredità 2006[35]	30	• Bilateral TT* (n=15) • Bilateral myringotomy (contact-diode laser) (n=15)	Laterality NR (OME duration ≥3 months)	Not required (baseline hearing levels NR)	-	2 – 6 yrs. (3.7 yrs.)	47%	-	1 mos. (% NR) 2 mos. (% NR) 3 mos. (% NR) 12 mos. (% NR)	CoE III
Gates 1987, 1989[48,49]	578	• Bilateral‡ TT (n=150) • Bilateral‡ myringotomy (n=127) • (Bilateral TT‡ + Ad, n=150) • (Ad, n=151)	Laterality of effusion at surgery: bilateral (66%), unilateral (20%), no effusion (14%)§; (chronic OME; duration not further specified)	Not required (baseline hearing levels NR)	-	4 – 8 yrs. (NR yrs.; 69% of patients in these groups were age 6 – 7 yrs.§)	59%§	-	24 mos. (67%)	CoE II
Mandel 1989[88] (no hearing loss group only‡‡)	86 ‡‡	• TT • (n=30) • Myringotomy (n=27) • (WW/delayed surgery n=29)	Bilateral (68%) or unilateral (32%) (≥ 2 months)	No significant hearing loss (≤20dB if bilateral or ≤40dB if unilateral)	-	0.6 – 12 yrs. (NR§§)	44%	-	2 mos. (NR) 12 mos. (NR) 24 mos. (NR) 36 mos. (85%§§)	CoE III
Mandel 1989[88] (hearing loss group only‡‡	23 ‡‡	• TT • (n=11) • Myringotomy (n=12)	Bilateral (87%) or unilateral (13%) (≥ 2 months)	Significant hearing loss (>20dB if bilateral or	-	0.6 – 12 yrs. (NR§§)	17%	-	2 mos. (NR) 12 mos. (NR) 24 mos. (NR) 36 mos. (85%§§)	CoE III

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
				>40dB if unilateral) or symptoms of otalgia or vertigo not responsive to medicine						
Mandel 1992[89]	111	• TT (n=37) • Myringotomy (n=39) • (WW/delayed surgery n=35)	Bilateral (59%) or unilateral (41%) (≥ 2 months)	Not required, hearing level ≤35 dB	-	0.6 – 12 yrs. (NR§§)	33%	-	12 mos. (NR) 24 mos. (NR) 36 mos. (87%)	CoE III
TT versus Myringotomy: randomized by ear										
Black 1990[14]	149	• Unilateral TT, contralateral myringotomy, (n=37) • (Unilateral TT, contralateral no treatment, n=37) • (Ad + unilateral TT, contralateral myringotomy n=37) • (Ad + unilateral TT, contralateral no treatment n=38)	Bilateral (duration NR)	Not required (mean hearing level at baseline: 28.4 dB)	-	4 – 9 yrs. (6.1 yrs.)	35%	-	1.75 mos. (% NR) 6 mos. (% NR) 12 mos. (85%) 24 mos. (61%)	CoE II

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
Kent 1989[73]	30	• Unilateral TT (30 ears) • Unilateral thermal myringotomy (30 ears)	Bilateral (≥3 months)	Not required (mean hearing level at baseline NR, 80% had "deafness" at baseline)	-	1.5 – 12 yrs. (5.3 yrs.)	47%	-	1 mos. (% NR) 2 mos. (% NR) 3 mos. (% NR) 6 mos. (% NR)	CoE III
Koopman 2004[76]	230	• Unilateral TT* (208 ears§) • Unilateral laser myringotomy (208 ears§)	Bilateral (duration NR)	Hearing impairment (not defined) for ≥3 mos. required (median 6 mos.)	-	NR – 11 yrs. § (4.2 yrs.)	48%§	-	6 mos. (67%)	CoE II
Cohort Studies										
(none)										

F/U: follow-up; NR: not reported; pop.: population

* D'Eredità, Koopman: in the TT group cold knife myringotomy was performed prior to tube insertion (rather than laser myringotomy as performed in the control group)

‡Gates 1987, 1989: procedures were bilateral unless one ear had been completely normal on all preoperative exams; the percentage of patients treated unilaterally was not reported.

§Demographics reported after exclusion of patients enrolled but did not undergo surgery: Gates: 15% of patients (41/277); Koopman: 9.6% of patients (22/230).

**Black 1990: A total of 149 patients were enrolled; patients were randomized to one of four groups: unilateral TT and no treatment in contralateral ear (n=37), unilateral TT and myringotomy in contralateral ear (n=37), adenoidectomy plus unilateral TT and no treatment in contralateral ear (n=38), adenoidectomy plus unilateral TT and myringotomy in contralateral ear (n=37). Randomization for which ear received TT insertion was performed subsequently. The adenoidectomy groups are included in the section comparing tubes + other treatment to other treatment alone.

‡‡ Mandel 1989: A total of 109 patients were enrolled and first stratified according to the absence (n=23) or presence (n=86) of hearing loss ((>20dB bilaterally or >40dB unilaterally or speech awareness threshold >20dB higher than appropriate for age); patients were randomized within these groups to treatments as follows.

§§ Mandel 1989: 85% f/u for all 109 patients in study.

Table 12. Intervention details: TT vs. Myringotomy for OME

Study	Interventions (n)	Treatment Protocol	Indication for tube (re)insertion	Tube (re)insertion (%)
RCTs				
D'Eredità 2006[35]	TT* (n=15)	• General anesthesia • Bilateral • Teflon Shah mini vent tubes	• NR	• NR
	Myringotomy (contact-diode laser) (n=15)	• General anesthesia • Bilateral • Contact-diode laser myringotomy (2.5mm)	• NR	• NR
Gates 1987, 1989[48,49]	TT (n=150)	• General anesthesia • Bilateral* • Shepard tubes	• Reinsertion: Persistent effusion and hearing level in better ear ≥20 dB after 12 weeks of antibiotics and decongestants • TT+adenoidectomy performed if fluid re-appeared and persisted after second TT procedure	• ≤24 months: • Any surgical retreatment†: 24.0% (31/129) • 1 surgical retreatment†: 20% (29/129) • 2 surgical retreatments†: 4% (5/129) • 3 surgical retreatments†: 0% (0/129)
	Myringotomy (n=127)	• General anesthesia • Bilateral* • Myringotomy details NR	• TT+adenoidectomy: if effusion re-appeared and persisted after second myringotomy procedure • (Second myringotomy performed if there was persistent effusion and hearing level in better ear ≥20 dB after 12 weeks of antibiotics and decongestants)	• ≤24 months: • Any surgical retreatment†: 45.8% (49/107) • 1 surgical retreatment†: 32% (34/107) • 2 surgical retreatments†: 12% (13/107) • 3 surgical retreatments†: 2% (2/107)
Mandel 1989[88] (no hearing loss group only)	TT (n=30)	• General anesthesia • Unilateral (30%) or bilateral (70%)	• Bilateral middle ear effusion and significant hearing loss at three	• 0-12 mos.: 15% (4/27) • 12-24 mos.: 33% (9/27)

Study	Interventions (n)	Treatment Protocol	Indication for tube (re)insertion	Tube (re)insertion (%)
		• Armstrong tubes	consecutive monthly visits (i.e., over 2 months).	• 24-36 mos.: 8% (2/25)
	Myringotomy (n=27)	• General anesthesia • Unilateral (33%) or bilateral (67%) • Myringotomy: wide circumferential incision	• Within one year of a second myringotomy, and with bilateral middle ear effusion and significant hearing loss at three consecutive monthly visits (i.e., over 2 months).	• 0-12 mos.: 69% (18/26) • 12-24 mos.: NR • 24-36 mos.: NR
Mandel 1989[88] (hearing loss group only)	TT (n=11)	• General anesthesia • Unilateral (9%) or bilateral (91%) • Armstrong tubes	• Bilateral middle ear effusion and significant hearing loss at three consecutive monthly visits (i.e., over 2 months).	• 0-12 mos.: 10% (1/10) • 12-24 mos.: 44% (4/9) • 24-36 mos.: 44% (4/9)
	Myringotomy (n=12)	• General anesthesia • Unilateral (17%) or bilateral (83%) • Myringotomy: wide circumferential incision	• Within one year of a second myringotomy, and with bilateral middle ear effusion and significant hearing loss at three consecutive monthly visits (i.e., over 2 months).	• 0-12 mos.: 67% (8/12) • 12-24 mos.: NR • 24-36 mos.: NR
Mandel 1992[89]	TT (n=37)	• General anesthesia • Unilateral (43%) or bilateral (57%) • Armstrong tubes	• Treatment failure: Bilateral (unilateral) middle ear effusion persisting for 4 (6) months.	• 0-12 mos.: 3% (1/34) • 12-24 mos.: 23% (7/30) • 24-36 mos.: 21% (6/28) •
	Myringotomy (n=39)	• General anesthesia • Unilateral (38%) or bilateral (62%) • Myringotomy: wide circumferential incision •	• same	• 0-12 mos.: 92% (33/36) • 12-24 mos.: 27% (9/34) • 24-36 mos.: 16% (5/31)
Black 1990[14]	TT (37 ears)	• Anesthesia NR • Unilateral	• At discretion of treating otolaryngologist, who were asked by investigators to	• NR

Study	Interventions (n)	Treatment Protocol	Indication for tube (re)insertion	Tube (re)insertion (%)
		• Tube type NR	avoid surgical treatment whenever possible	
	Myringotomy (37 ears)	• Anesthesia NR • Unilateral • Myringotomy details NR	• same	• NR
Kent 1989[73]	TT (30 ears)	• Anesthesia NR • Unilateral • Tube type NR	• NR	• NR
	Myringotomy (30 ears)	• Anesthesia NR • Unilateral • Thermal myringotomy	• NR	• NR
Koopman 2004[76]	TT* (208 ears)	• General anesthesia • Unilateral • Donaldson tube	• NR	• ≤6 months: 5.2%
	Myringotomy (208 ears)	• General anesthesia • Unilateral • Laser myringotomy	• NR	• ≤6 months: 5.7%

F/U: follow-up; NR: not reported; pop.: population

*Gates 1987, 1989: procedures were bilateral unless one ear had been completely normal on all preoperative exams; the percentage of patients treated unilaterally was not reported.

†Gates 1987, 1989: most surgical retreatments were done according to the protocol, however patients were able to select an alternative treatment (further details NR)

Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G18-G27).

Clinical outcomes

Hearing levels
Four trials reported hearing levels: Black[14] (CoE II) (mean age 6.1 years at enrollment), Gates[48,49] (CoE II) (age range 4-8 years at enrollment), D'Eredita[35] (CoE III) (mean age 3.7 years at enrollment), and Kent[73] (CoE III) (mean age 5.3 years at enrollment). None of the studies required hearing loss at baseline; Black[14] reported a mean hearing level at baseline of 28.4 dB, and Kent[73] reported that 80% had "deafness" (not defined) at baseline). Results are available in table format in Appendix Table G18.

At six months, two trials reported better hearing in the TT ear compared with the myringotomy ear: Black[14] reported a mean improvement in hearing of 7.4 dB (95% CI, 1.4 to 13.4, p<0.05), and Kent[73] reported that significantly fewer TT ears had "hearing impairment" (not defined) than those treated with thermal myringotomy alone (0% versus 17%, RD -17%, 95% CI -30% to -3%, p=0.0206). By 12 months, no statistically significant differences were found: Black[14] reported mean hearing levels that were 3.7 dB better in the TT ear (95% CI -0.4 to 7.8), and D'Eredita 2006[35] reported that hearing levels were normal in all patients at 12 months. Results were less clear at 24 months, with one trial (Black[14]) reporting no statistical difference between ears (0.9 dB better in the TT ear, 95% CI -2.7 to 4.6) and another trial (Gates[48,49]) reporting that TT patients had hearing loss (hearing levels ≥20 dB) at 7% to 8% fewer audiometry evaluations from baseline through 24 months than myringotomy patients (better ear: 10.1 ± 14.1% vs. 18.6 ± 19.5% of visits, RD -8.5%, 95% CI -12.5% to -4.5%, p<0.001) (worse ear: 30.4 ± 22.7% vs. 37.5 ± 25.3% of visits, RD -7.1%, 95% CI -12.8% to -1.4%, p=0.0145).

Otorrhea
Five trials reported otorrhea: D'Eredita[35] (CoE III) (mean age 3.7 years at enrollment), Gates[48,49] (CoE II) (age range 4-8 years at enrollment), Kent[73] (CoE III) (mean age 5.3 years at enrollment), Koopman[76] (CoE II) (mean age 4.2 years at enrollment) and Mandel 1989[88] (CoE III) (age range 0.6-12 years at enrollment). There were no statistically meaningful differences in otorrhea occurrence between TT and myringotomy through three months in two trials (D'Eredita[35], Kent[73]), through six months in one trial (Kent[73]), or through 24 months in one trial (Gates[48,49]); the latter study also reported no difference in the percentage of patients with one, two or three or more episodes of otorrhea through 24 months. One trial (Mandel 1989[88]) reported that patients in TT group had 0.26 to 0.27 more otorrhea episodes per year over three years than myringotomy patients, but the statistical significance was not reported. Results are available in table format in Appendix Table G19.

AOM episodes
Three trials reported AOM recurrence: Mandel 1989[88] (CoE III) and Mandel 1992[89] (CoE III) (age range of both was 0.6-12 years at enrollment), and Gates[48,49] (CoE II) (age range 4-8 years at enrollment). Through the first 12 months, patients in the TT group had 0.58 fewer AOM episodes than the myringotomy group during the first 12 months (0.23 versus 0.81 AOM episodes per patient, p<0.001) as reported by one trial (Mandel 1992[89]). Over the first 36 months, however, results across two trials were less clear, with one (Mandel 1989[88]) reporting that the TT group had 0.26 fewer (0.24 vs. 0.50 episodes per year) and the other (Mandel 1992[89]) reporting only 0.06 fewer AOM episodes per year over the first 36 months (0.51 versus 0.57 AOM episodes per year). The statistical significance of the results over the first three years was not reported by either study. Through 24 months, one trial (Gates[48,49]) reported that AOM occurred in a similar proportion of appointments in TT versus myringotomy patients (4.1% ±

5.9% vs. 4.5% ± 5.2% of appointments, RD -0.4%, 95% CI -1.8% to 1.0%, p=NS). Similarly, there was no difference in the cumulative incidence of AOM between groups (35.7% vs. 44.9%, RD -9.2%, 95% CI -21.7% to 3.3%).

AOM or OME recurrence

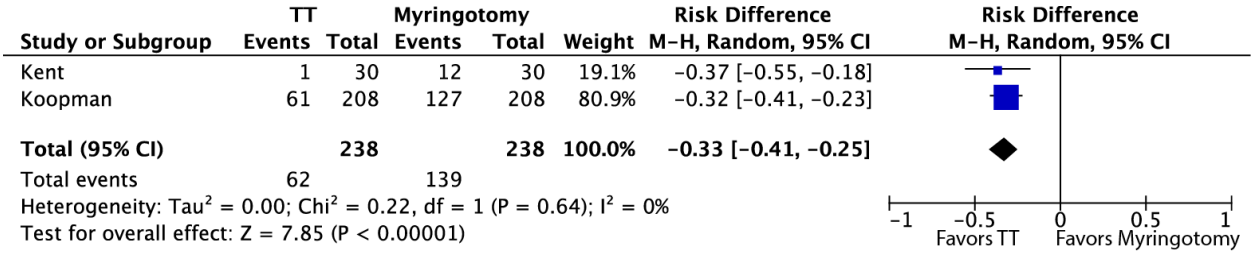
Three trials reported effusion of either AOM or OME: Mandel 1989[88] (CoE III) and Mandel 1992[89] (CoE III) (age range of both was 0.6-12 years at enrollment), and Gates[48,49] (CoE II) (age range 4-8 years at enrollment). Overall, results suggest that the frequency of either AOM or OME is lower in the first year of follow-up in the TT versus the myringotomy group as well as cumulatively over three years follow-up. Over the first year of follow-up, patients in the TT group spent 9.8% to 17% of time with AOM or OME, while the myringotomy group spent 56.6% to 61% of time with either condition (range of means, p≤0.01 for each study) (Mandel 1989[88], Mandel 1992[89]). Over the entire first three years of follow-up, patients in the TT group had effusion 21% to 31% of the time, while those treated with myringotomy alone had AOM or OME 38% to 41% of the time (risk difference ranged from -10% to -20%); the statistical significance of these results were not reported.

Between baseline and 24 months, one trial (Gates[48,49]) reported that AOM or OME effusion was present in TT patients at 14.2% (95% CI, 7.9% to 20.5%) fewer follow-up appointments compared with myringotomy patients (34.9% ± 23.5% vs. 49.1% ± 20.5% appointments, p<0.0001). Further, the median time to first AOM or OME recurrence was significantly longer in TT patients (222 ± 11 vs. 54 ± 2 days, p<0.0001).

OME recurrence

Recurrence of OME was reported by four trials: Kent[73] (CoE III) (mean age 5.3 years at enrollment), Koopman[76] (CoE II) (mean age 4.2 years at enrollment), Gates[48,49] (CoE II) (age range 4-8 years at enrollment), and D'Eredita[35] (CoE III) (mean age 3.7 years at enrollment). At three months, one larger trial (N=208) reported significantly fewer cases of effusion in the TT ear versus the myringotomy ear (18.5% versus 62.9%, RD -44.7%, -53.1% to -36.3%, p<0.001) while one small trial (Kent[73], N=30) found no difference in the percentage of TT versus myringotomy ears with effusion (0% versus 7%, RD -7%, -16% to 2%, p=0.1538). It was unclear what could account for the large differences in effusion incidence between these two trials. At six months, pooled results from both trials (Kent[73] and Koopman[76]) suggest that TT ears were associated with significantly less effusion compared with myringotomy ears (RD, -33%, 95% CI -41% to -25%, p<0.00001, I^2=0%) (Figure 15). In contrast, D'Eredita[35] reported that both TT and myringotomy groups had complete resolution of OME at six and 12 months checkups. Gates[48,49]

Figure 15. OME recurrence by ear at 6 months: TT (unilateral) vs. myringotomy (contralateral) for OME



Through 24 months, one trial (Gates[48,49]) reported that TT patients had OME at significantly fewer appointments than myringotomy patients (31.8% ± 23.2% vs. 46.6% ± 24.5% of appointments, RD -

14.8%, 95% CI -20.9% to -8.7%, p<0.0001). However, there was no difference between groups in the overall incidence of OME (85.3% vs. 89.7%, RD -4.5%, 95% CI -12.9% to 4.0%).

Balance and coordination
None of the included studies reported this outcome.

Cholesteatoma
One trial (Gates[48,49]) reported that no cholesteatomas formed through 24 months. Mandel 1992[89] reported no cases of cholesteatoma in TT patients (0/37) and two cases in myringotomy patients (5% (2/39)) through 36 months, a difference which was not statistically significant. One child was treated with tympanomastoid surgery and the other underwent TT insertion.

Functional and quality of life outcomes

Auditory processing
Auditory processing was evaluated by two RCTs: Mandel 1989[88] (CoE III) and Mandel 1992[89] (CoE III); patients ranged in age from 0.6 to 12 years. Although the noise threshold for speech recognition was 2.0 to 3.4 dB higher in the TT group at baseline, the speech recognition threshold was 3 to 21.2 dB lower in the TT group (range, 5.5-12.5 dB) compared with the WW group (range, 14.8 to 26.7 dB) at one, two, and four months follow-up, although the statistical significance of this result was not reported (and could not be calculated) (Mandel 1989[88], Mandel 1992[89]). See Appendix Table G23 for detailed data.

Subanalysis: hearing levels in patients stratified by the presence of middle ear effusion
Both trials reported that speech-recognition thresholds measured at any point during the course of the study (up to three years) were lower in both TT and WW groups in patients with either a functional tube or without middle ear effusion (in patients without an intact tube) (range across TT and myringotomy groups, 4.5 to 8.5 dB) compared with those in which middle ear effusion was present (range across TT and myringotomy groups, 17.5 to 26.3 dB) (p<0.001 for both studies) (Mandel 1989[88], Mandel 1992[89]). The differences between the TT and myringotomy groups were small, ranging from 0.5 to 2.7 dB lower in the TT group.

Pain
One trial (Kent[73] (CoE III) (mean age 5.3 years at enrollment) reported that earache occurred in a similar percentage of TT and myringotomy ears at 1, 2, 3, and 6 months follow-up (range of mean differences: 0% to 13% fewer cases in the TT group, p=NS for all).

Other functional and quality of life outcomes
None of the included studies reported any other functional or quality of life outcomes, including attention and behavioral outcomes, academic achievement, speech and language development, parent or patient satisfaction with treatment/outcomes, or patient and parent quality of life.

Functional and quality of life outcomes
Surgery
Details on repeat surgery or tube insertion were provided by four trials (Gates[48,49] (CoE II) (age range 4-8 years at enrollment), D'Eredita[35] (CoE III) (mean age 3.7 years at enrollment), Mandel 1989[88] (CoE III) and Mandel 1992[89] (CoE III) (patients ranged in age from 0.6 to 12 years).

Tube reinsertion in the TT group or tube placement in the myringotomy group was reported by two trials: Mandel 1989[88] and Mandel 1992[89]. During the first year follow-up, TT patients were 55% less likely to undergo surgery (reinsertion) than myringotomy patients (initial tube placement) (3-14% vs. 61-64%) (pooled RD -55%, 95% CI, -69% to -41%, p<0.0001, I^2=16%) (Figure 16). However, there was no difference in tube placement between groups in the second year of follow-up (i.e., 12-24 months), with 23-36% of TT patients undergoing tube placement versus 26-47% in the myringotomy group (pooled RD -7%, 95% CI, -22% to 9%, p=0.63, I^2=0) (Figure 17), or in the third year of follow-up (i.e., 24-36 months) (18-22% versus 16-35%, pooled RD -1%, 95% CI, -15% to 13%, p=0.91, I^2=0) (Figure 18) based on two small trials. Results are also available in Appendix Table G25.

Figure 16. Surgery (tube placement) through 12 months: TT vs. Myringotomy for OME

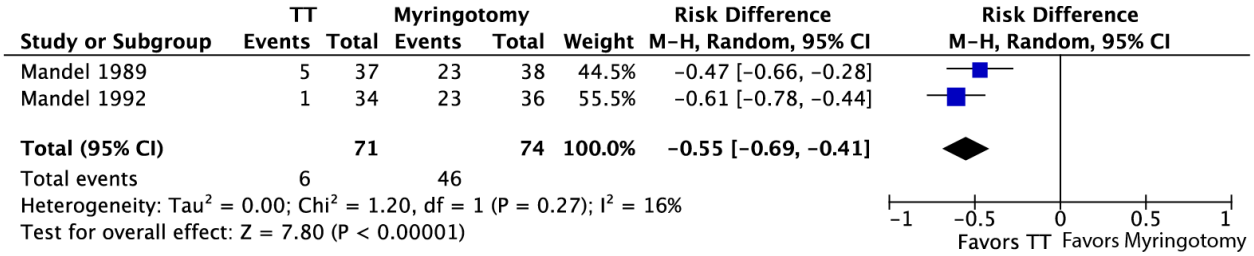


Figure 17. Surgery (tube placement) between 12-24 months: TT vs. Myringotomy for OME

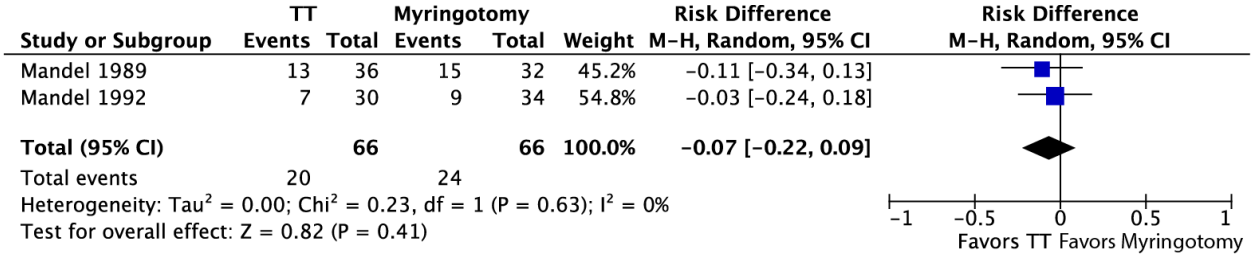
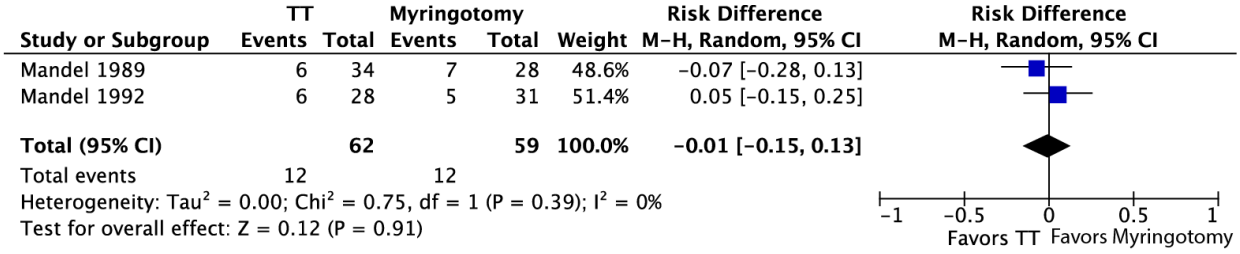


Figure 18. Surgery (tube placement) between 24-36 months: TT vs. Myringotomy for OME



Gates[48,49] reported that 21.8% fewer TT patients underwent surgical retreatment through 24 months than myringotomy patients; surgical retreatments were typically performed according to protocol, though patients were permitted to select another treatment (further details not reported) The same trial also reported the number of surgical retreatments through 24 months was significantly lower in the TT group (36 vs. 66, p<0.001).

D'Eredita[35] reported that there was no difference between TT and myringotomy groups in myringoplasty procedures through 12 months (7% versus 0%, p=NS).

Medication usage

Medication usage was reported by one trial (Gates[48,49] (CoE II) (age range 4-8 years at enrollment). There was no difference between TT and myringotomy patients in the need for medical retreatment for OME; however, TT patients required on average 0.75 (0.31 to 1.19) fewer courses of medical treatment for OME than myringotomy patients (2.55 ± 1.75 vs. 3.30 ± 1.69, p=0.0010). There was no difference between groups in need for medical treatment of AOM. Detailed data are available in Appendix Table G26.

Number of office visits

The need for unscheduled office visits for illness as well as the mean number of unscheduled office visits for illness per child were reported to be similar between groups in one trial (Gates[48,49] (CoE II) (age range 4-8 years at enrollment). Detailed data are available in Appendix Table G27.

4.1.5. OME: Tubes + Adenoidectomy vs. Myringotomy + Adenoidectomy

Studies included

Eight RCTs reported across nine publications[14,24,48,49,125,142,152,158,169] met the inclusion criteria. Of these, four trials randomized patients to either bilateral TT or myringotomy and treated all patients with adenoidectomy (Casselbrant 2009[24], Gates 1987/1989[48,49], Popova 2010[125]) or adenotonsillectomy (Vlastos 2011[169]) and four trials randomized children by ear to unilateral TT and contralateral myringotomy and treated all patients with adenoidectomy (Black 1990[14], Ruckley 1988[142], Shishegar 2007[152], To 1984[158]). In addition, two prospective cohort studies published across five papers[16,74,81,160,161 #825] met the inclusion criteria and performed by-ear (rather than by-child) analysis, treating all patients with adenoidectomy (Tos 1983/1989, Bonding 1985, Khodaverdi 2013[16,74,160,161]) or adenotonsillectomy (Leek 1979[81]) and performing TT insertion in one ear and myringotomy in the opposite ear. One retrospective cohort study was also included (Caye-Thomasen 2008[26]) and treated all patients with adenoidectomy (and tonsillectomy in some patients) and performed TT insertion in one ear and myringotomy in the contralateral ear.

Study characteristics

Of the included trials, four randomized by patient (N=52-578) and were published between the years 1987 and 2011 (Casselbrant[24], Gates[48,49], Popova[125], Vlastos[169]) while four randomized by ear (N = 30 to 149) and were published between 1984 and 2007 (Black[14], Ruckley[142], Shishegar[152], To[158]); all patients/ears underwent adenoidectomy plus either TT insertion or myringotomy. In the trials randomized by patient, mean patient ages ranged from 2.9 to 5.1 years across three (mean age not reported by Gates[48,49]) while females comprised 41% to 66% of children. In the trials that randomized by ear, mean age ranged from 5.1 to 7.5 years across three trials (mean age not reported by Shishegar[152]) and 35% to 46% of the children were female. For those trials that randomized by patient, two (Popova[125], Vlastos[169]) included only children with bilateral OME (≥3 months in one and duration not specified in the other), one trial (Casselbrant[24]) included both bilateral (≥3 months duration) and unilateral (≥6 months duration) OME, and one included both bilateral and unilateral OME as well as patients with no effusion on presentation (Gates[48,49]); the latter trial indicated that OME was chronic but did not specify duration further. All four trials that randomized by ear included only patients with bilateral OME; two did not require a specific OME duration (Black[14], Ruckley[142]) and two included only

chronic OME but did not provide any details on duration (Shishegar[152], To[158]). Hearing loss was required in two of the trials that randomized by patient (Popova[125], Vlastos[169]); the other two did not require hearing loss and did not report baseline hearing levels in their patients. Only one of the trials that randomized by ear required hearing loss (To[158]); however, mean baseline hearing levels in the remaining three trials suggested that, in general, patients had hearing loss. Overall, only one trial (randomization by patient) required additional symptoms for inclusion which was sleep disordered breathing (Vlastos[169]). Study characteristics, including quality assessment ratings, are summarized in Table 13. Two prospective cohort studies, published between 1979 and 2013, included 72 and 224 children treated by ear with this comparison. Mean patient age was 3.9 years in one study (Tos, Bonding, Khodaverdi[16,74,160,161]) and ages ranged from 2 to 15 years in the other (Leek[81]). Females comprised 41% and 33% of the populations, respectively. Both studies included only bilateral OME; one required at least three months duration (Tos, Bonding, Khodaverdi[16,74,160,161]) and the other did not specify a duration period. Hearing loss was not required in one cohort although mean baseline hearing levels indicated that most children had hearing loss (Tos, Bonding, Khodaverdi[16,74,160,161]); the other study did not report hearing loss. In one study, patients were also required to have enlarged adenoids causing upper airway obstruction (Leek[81]). One retrospective cohort study published in 2008 was also included and compared TT with myringotomy in children treated by ear (Caye-Thomasen 2008[26]). A total of 224 patients (mean age 3.9 years; 41% female) with bilateral OME of at least 3 months duration were enrolled. Hearing loss was not required though the baseline mean hearing level (27.4 dB) suggested overall hearing loss. No other additional symptoms were required. The authors focused their results on the 168 patients (336 ears) (75% of population) who received only the initial treatment (to avoid potential confounding due to difference in disease severity and the influence of repeat treatment).

Intervention details are summarized in Table 14. Briefly, patients underwent surgery with general anesthesia. Three (Black[14], Shishegar[152], To[158]) of the four trials that randomized by ear and all three cohort studies did not specify the use of general anesthesia, however, there was no indication otherwise. All patients underwent adenoidectomy; with simultaneous tonsillectomy in one trial (Vlastos[169]) and in one prospective cohort (Leek[81]). In the retrospective cohort, tonsillectomy was performed in 41 (18%) children (Caye-Thomasen 2008[26]). For those trials that randomized by patient, children received either bilateral tube placement (Casselbrant[24] did not report the laterality of TT) or bilateral myringotomy. For those trials that randomized by ear, and for all three cohort studies, children received TT insertion in one ear and myringotomy in the contralateral ear. No study specifically forbade tube reinsertion. Indications for tube reinsertion varied across the trials that randomized by patient and included bilateral or unilateral effusion for prespecified durations (Casselbrant[24]); persistent effusion and hearing loss after 12 weeks of medical therapy (Gates[48,49]); and premature extrusion (Popova[125]). Only two of the studies that randomized by ear reported indications for tube reinsertion, which was avoided if at all possible in one trial (Black[14]) and permitted following the development of a retraction segment in the other (To[158]). All cohort studies allowed tube reinsertion or insertion in the event of recurrent or persistent OME; two further required hearing impairment of at least 3 months (Tos, Bonding, Khodaverdi[16,74,160,161],Caye-Thomasen 2008[26]) (reinsertion rates are reported in Table 14.

Table 13. Study characteristics and patient demographics: TT plus adenoidectomy vs. Myringotomy + adenoidectomy for OME

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
TT + adenoidectomy versus Myringotomy + adenoidectomy:: randomized by patient										
Casselbrant 2009[24]	99	• TT* + Ad (n=32) • Myringotomy* + Ad (n=34) • (TT,* n=32)	Bilateral OME ≥3 months OR unilateral OME ≥6 months (or ≥3 months if one TT extruded and other intact)	Not required (baseline hearing levels NR)	None required (63% had nasal obstruction ; 35% had previous TT insertion)	2.0 – 3.9 yrs. (2.9 yrs.)	66%	-	18 mos. (67%) 36 mos. (59%)	CoE III
Gates 1987, 1989[48,49]	578	• Bilateral† TT + Ad (n=150) • Bilateral myringotomy + Ad (n=151) • (Bilateral† TT n=150) • (Bilateral† myringotomy n=127)	Laterality of effusion at surgery: bilateral (66%), unilateral (20%), no effusion (14%)§; (chronic OME; duration not further specified)	Not required (baseline hearing levels NR)	-	4 – 8 yrs. (NR yrs.; 74% of patients in these groups were age 6 – 7 yrs.‡)	41%‡	-	24 mos. (67%)	CoE II
Popova 2010[125]	90	• Bilateral TT + Ad (n=42§) • Bilateral myringotomy + Ad (n=36§)	Bilateral (≥3 months)	Hearing loss required (>20 dB)	-	3 – 7 yrs. (5.1 yrs.§)	46%§	-	12 mos. (87%)	CoE III
Vlastos 2011[169]	52	• Bilateral TT + Ad + Tons (n=25)	Bilateral (duration not specified)	Hearing loss required (30-55 dB)	Sleep disordered breathing	3 – 7 yrs. (4.5 yrs.)	44%	Sleep apnea	12 mos. (79%)	

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
		• Bilateral myringotomy + Ad + Tons (n=27)								
TT + adenoidectomy versus Myringotomy + adenoidectomy: randomized by ear										
Black 1990[14]	149	• Ad + unilateral TT, contralateral myringotomy (n=37) • (Ad + unilateral TT, contralateral no treatment, n=38) • (Unilateral TT, contralateral myringotomy, n=37) • (Unilateral TT, contralateral no treatment, n=37)	Bilateral (duration NR)	Not required (mean hearing level at baseline: 28.5 dB)	-	4 – 9 yrs. (6.1 yrs.)	35%	-	1.75 mos. (% NR) 6 mos. (% NR) 12 mos. (85%) 24 mos. (61%)	CoE II
Ruckley 1988[142]	40	• Ad + unilateral TT, contralateral thermal myringotomy (n=40)	Bilateral (duration NR)	Not required (mean hearing level at baseline: 21.2 dB)	-	4 – 9 yrs. (5.1 yrs.)	43%	-	3 mos. (90%)	CoE II

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
Shishegar 2007[152]	30	• Ad + unilateral TT, contralateral myringotomy (n=30)	Bilateral (chronic (not defined))	Not required (mean hearing level at baseline: 25.7 dB)	-	4 – 8 yrs. (NR)	37%	-	6 mos. (% NR)	CoE III
To 1984[158]	54	• Ad** + unilateral TT, contralateral myringotomy (n=54)	Bilateral (chronic (not defined))	Hearing loss required (mean hearing level at baseline: 33.5 dB)	-	3.9 – 14 yrs. (7.5 yrs.)	46%	-	Mean 24 mos. (range, 12-60 mos.) (% NR)	CoE III
Cohort studies										
Leek 1979[81]	72	• Ad-Tons + unilateral TT, contralateral myringotomy (n=72)	Bilateral (duration NR)	NR	Enlarged adenoids causing upper airway obstruction	2 – 15 yrs. (NR, 95% were aged 3 – 9 yrs.)	33%	-	Mean 19 mos. (100%)	CoE III
Tos 1983, Bonding 1985, Tos 1989, Khodaverdi 2013[16,74,160,161]	224	• Ad + unilateral TT, contralateral myringotomy (n=224)	Bilateral (≥3 mos.)	Hearing loss not required (mean hearing level at baseline: 28 dB; 78% ears had hearing levels >20 dB at baseline)	-	0.9-13 yrs. (3.9 yrs.)	41%	-	12-36 mos. (86%) 72-84 mos. (65%) 300 mos. (46%)	CoE III
Caye-Thomasen 2008[26]	168 ††	• Adenoidectomy plus: • TT (n=168 right ears) • Myringotom	Bilateral (≥ 3 months)	Not required. Mean baseline hearing levels (PTA):	None	0.9–13 yrs. (3.9 years) ††	41%††	No	• 3 years (87%; 146/168) • 7 years (68%; 115/168) • 25 years (48%;	CoE III

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
		y only (n=168 left ears) • *41 patients had tonsillectomy (NR by treatment groups)		TT: 28.8 Myringotomy: 26 p<0.01					80/168)	

Ad: adenoidectomy; Ad-Tons: adenotonsillectomy; F/U: follow-up; NR: not reported; pop.: population

*Casselbrant: laterality of TT insertion and myringotomy NR

†Gates 1987, 1989: procedures were bilateral unless one ear had been completely normal on all preoperative exams; the percentage of patients treated unilaterally was not reported.

‡Demographics reported after exclusion of patients enrolled but did not undergo surgery: Gates: 15% of patients (46/301)

§Data reported only for those with complete follow-up

**19% (10/54) did not undergo adenoidectomy: 9 had previously received adenoidectomy and 1 did not have adenoids

†† A total of 224 patients were included; however, the authors focused their results on the 168 who received only the initial treatment. Demographics were not reported separately and represent all 224 patients.

Table 14. Intervention details: TT plus adenoidectomy vs. Myringotomy + adenoidectomy for OME

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Casselbrant[24]	TT + Ad (n=32)	• Anesthesia NR • Laterality NR • Teflon Armstrong tubes • Adenoidectomy	• Bilateral effusion for 4 consecutive months or for 6 of previous 12 months; OR unilateral effusion for 6 consecutive months or for 8 of previous 12 months	• ≤18 mos.: 10% (3/32) • ≤36 mos.: 29% (9/32)
	Myringotomy + Ad (n=34)	• General anesthesia • Bilateral myringotomy	• same	• ≤18 mos.: 24% (8/34) • ≤36 mos.: 24% (8/34)

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
		• Adenoidectomy		
Gates[48,49]	TT + Ad (n=150)	• General anesthesia • Bilateral • Shepard tubes • Adenoidectomy	• Reinsertion: Persistent effusion and hearing level in better ear ≥20 dB after 12 weeks of antibiotics and decongestants •	• ≤24 months: • Any surgical retreatment*: 11.2% (14/125) • 1 surgical retreatment*: 9.6% (12/125) • 2 surgical retreatments*: 0.8% (1/125) • 3 surgical retreatments*: 0.8% (1/125)
	Myringotomy + Ad (n=151)	• General anesthesia • Bilateral myringotomy • Adenoidectomy	• TT: if effusion re-appeared and persisted after second myringotomy procedure • (Second myringotomy performed if there was persistent effusion and hearing level in better ear ≥20 dB after 12 weeks of antibiotics and decongestants)	• ≤24 months: • Any surgical retreatment*: 11.5% (15/130) • 1 surgical retreatment*: 10.0% (13/130) • 2 surgical retreatments*: 1.5% (2/130) • 3 surgical retreatments*: 0% (0/130) •
Popova[125]	TT + Ad (n=42†)	• General anesthesia • Bilateral Donaldson tubes • Adenoidectomy	• Premature extrusion	• ≤12 mos.: 2% (1/42) •
	Myringotomy + Ad (n=36†)	• General anesthesia • Bilateral myringotomy • Adenoidectomy	• NR	• NR
Vlastos[169]	TT + Ad-Tons (n=25)	• General anesthesia • Bilateral Shepard tubes • Adenotonsillectomy	• NR	• NR

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
	Myringotomy + Ad-Tons (n=27)	• General anesthesia • Bilateral myringotomy • Adenotonsillectomy	• NR	• ≤12 mos.: 15% (4/27) •
Black[14]	TT + Ad (37 ears)	• Anesthesia NR • Unilateral TT (type NR) • Adenoidectomy •	• At discretion of treating otolaryngologist, who were asked by investigators to avoid surgical treatment whenever possible	• NR
	Myringotomy + Ad (37 ears)	• Anesthesia NR • Unilateral myringotomy • Adenoidectomy	• Same	• NR
Ruckley[142]	TT + Ad (40 ears)	• General anesthesia • Unilateral Shepard tube • Adenoidectomy	• NR	• NR
	Myringotomy + Ad (40 ears)	• General anesthesia • Unilateral thermal myringotomy • Adenoidectomy	• NR	• ≤3 mos.: 18% (7/40) •
Shishegar[152]	TT + Ad (30 ears)	• Anesthesia NR • Unilateral Shepard tube • Adenoidectomy	• NR	• NR
	Myringotomy + Ad (30 ears)	• Anesthesia NR • Unilateral myringotomy • Adenoidectomy	• NR	• NR
To[158]	TT + Ad (54 ears)	• Anesthesia NR • Unilateral Shepard tube • Adenoidectomy	• Development of a retraction segment	• ≤24 mos.: 4% (2/54) •
	Myringotomy + Ad (54	• Anesthesia NR	• same	• ≤24 mos.: 2% (1/54)

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
	ears)	• Unilateral myringotomy • Adenoidectomy		•
Cohort Studies				
Leek[81]	TT + Ad-Tons (72 ears)	• Anesthesia NR • Unilateral flanged TT • Adenotonsillectomy	• Recurrent effusion	• ≤19 mos. (mean): 15% (11/72)
	Myringotomy + Ad-Tons (72 ears)	• Anesthesia NR • Unilateral myringotomy • Adenotonsillectomy	• same	• ≤19 mos. (mean): 21% (15/72)
Tos, Bonding, Khodaverdi 16,74,160,161	TT + Ad (224 ears)	• Anesthesia NR • Unilateral Donaldson tube • Adenoidectomy	• Recurrent OME with type B tympanograms and hearing impairment ≤3 months	• <12 mos.: NR • 12-36 mos.: 10% (23/224)
	Myringotomy + Ad (224 ears)	• Anesthesia NR • Unilateral myringotomy • Adenoidectomy	• same	• During "grommet period" (i.e., grommet functioning in contralateral ear): 14% (32/224) • 12-36 mos.: 9% (21/224)
Caye-Thomasen 2008[26]	TT (n=168 ears)	• Anesthesia NR • Bilateral myringotomy: radial orientation in the posteriorinferior quadrant, length 2 to 3 mm • Unilateral Donaldson tubes (right ear)	• Persisting or recurrent disease (laterality NR) (type B tympanogram and hearing impairment for at least 3 months during the follow-up period) received	• Follow-up time point NR • 10% (22/224)*
	Myringotomy (n=168 ears)	• Anesthesia NR • Bilateral myringotomy only: radial orientation in the posteriorinferior quadrant, length 2 to 3 mm	• same	• Follow-up time point NR • 21% (47/224)‡ • 2% (5/224)‡ had TT reinsertion after extrusion of the first tube in the left ear

Ad: adenoidectomy; Ad-Tons: adenotonsillectomy; F/U: follow-up; NR: not reported; pop.: population

*Gates 1987, 1989: most surgical retreatments were done according to the protocol, however patients were able to select an alternative treatment (further details NR)

†Data reported only for those with complete follow-up

‡Tube (re)insertion reported for entire population (224 children) only; n's back-calculated using percentages provided in text.

Results:
Detailed results tables for this section are available in Appendix G (Appendix G Tables G28-G44).

Clinical outcomes

Hearing
Three trials reported hearing levels by child: Gates[48,49] (mean age at enrollment not reported, age range 4-8 years, CoE II), Popova[125] (mean age 5.1 years at enrollment, CoE III), Vlastos[169] (sleep apnea patients, mean age 4.5 years at enrollment, CoE III). Four RCTs reported hearing levels by ear: Black[14] (mean age 6.1 years at enrollment, CoE II), Ruckley[142] (mean age 5.1 years at enrollment, CoE II), Shishegar[152] (mean age at enrollment not reported, age range 4-8 years, CoE III), and To[158] (mean age 7.5 years at enrollment, CoE III). All three cohort studies also reported hearing levels by ear: Leek[81] (mean age at enrollment not reported, age range 2-15 but 95% were age 3-9 years, CoE III), Tos/Bonding/Khodaverdi[16,74,160,161] (mean age 3.9 years at enrollment, CoE III), and Caye-Thomasen[26] (mean age 3.9 years at enrollment, CoE III).

By-child analysis
Two RCTs (Popova[125], Vlastos[169]) found no difference in mean hearing levels by child at 6 or 12 months; data were not pooled because one trial included sleep apnea patients only (Vlastos[169]) (Appendix Table G28). At 6 months, the mean difference between TT+Ad and myringotomy+Ad patients was 0.4 dB (95% CI -2.3 to 3.1 dB, p=NS) in the Popova[125] study and -5.2 dB (i.e., lower in the TT group) (95% CI -12.2 to 1.8 dB, p=NS) in the Vlastos[169] trial of sleep apnea patients. At 12 months, results were similar, with a mean difference in hearing levels of 0.8 dB (95% CI -1.2 to 2.8 dB) in the Popova[125] trial and -2.3 dB (95% CI -9.9 to 5.3 dB) in the Vlastos[169] trial of sleep apnea patients.

One trial (Gates[48,49]) reported no difference in the percentage of patients with hearing loss (hearing levels ≥20 dB) between groups through 24 months; results for TT+Ad and myringotomy+Ad were reported separately for the better ear (6.5% vs. 7.8% of patients had hearing loss, mean difference -1.3%, 95% CI -4.4% to 1.8%, p=NS) and the worse ear (22.4% vs. 22.0% of patients had hearing loss, mean difference 0.4%, 95% CI -5.3% to 6.1%, p=NS) (Appendix Table G28).

By-ear analysis
Except for a difference favoring the TT ear at 3 months in one trial, four trials reported similar hearing levels between TT+Ad and myringotomy+Ad ears at all time points evaluated. One trial (To[158]) found that hearing levels at 3 months were significantly better in the TT ear than the myringotomy ear (17.1 vs. 21.4 dB, mean difference -4.3 dB (95% CI not reported/calculable), p<0.05) however this difference was not sustained through 12 months (17.6 vs. 19.0 dB, p=NS) (Appendix Table G29). Another trial (Black[14]) reported no difference between TT and myringotomy ears at 6 months (mean difference -2.8 dB, 95% CI -7.4 to 1.9 dB, p=NS), 12 months (mean difference 1.0 dB, 95% CI -4.0 to 6.1 dB, p=NS), or 24 months (mean difference -0.7 dB, 95% CI -6.4 to 4.9 dB). Air bone gap hearing levels were similar between TT and myringotomy ears at 3 months in one trial (Ruckley[142]) (6.9 vs. 7.4 dB, mean difference -0.5 dB, 95% CI -2.4 to 1.4 dB, p=NS) and at 6 months in another trial (Shishegar[152]) (17.6 vs. 16.3 dB, mean difference 1.4 dB (95% CI not reported/calculable), p-value not reported) (Appendix Table G29).

One trial (To[158]) found that a similar proportion of TT and myringotomy ears in adenoidectomy patients had hearing levels that improved by more than 6 dB through 12 months (72% vs. 69% of ears, RD 4%, 95% CI -14% to 21%, p=NS) (Appendix Table G29).

One prospective cohort study (Tos/Bonding/Khodaverdi[16,74,160,161]) reported that mean hearing levels during the "grommet period" (defined as the period in which the tube was functioning in the TT ear) were significantly better in the TT ear compared with the myringotomy ear (12 vs. 18 dB, mean difference -6 dB, 95% -8 to -4 dB, p<0.001) (Appendix Table G29). This difference was not sustained after tube extrusion (14 dB in both ears), between 12 and 36 months (15 dB in both ears), or between 72 and 84 months (11.7 dB vs. 11.1 dB). The same study evaluated the percentage of ears in each treatment group that had hearing levels above various thresholds. At baseline, 85.1% of TT ears had hearing levels above 20 dB compared with 70.3% of myringotomy ears, a difference which was statistically significant (p=0.0022). Despite this baseline discrepancy that favored the myringotomy ear, significantly fewer TT ears had hearing levels above 20 dB compared with myringotomy ears during the grommet period (4.4% versus 31.1%, risk difference -26.7%, 95% CI -35.2% to -19.1%, p<0.0001). The differences were no longer statistically meaningful after tube extrusion or as measured between 12 and 36 months. Similar results were found for the percentage of patients with hearing levels above 30 dB and above 40 dB (at these thresholds there were not significant differences between groups at baseline) during the grommet period: >30 dB (1.5% vs. 19.3%, RD -17.8%, 95% CI -24.7% to -10.8%, p<0.001), >40 dB (0% vs. 7.4%, RD -7.4%, 95% CI -11.8 to -3.0%, p=0.0013). Again, results were similar between groups after the tubes had extruded through 36 months. In the retrospective cohort study (Caye-Thomasen[26]), hearing levels improved significantly more between baseline and three months in the TT ear versus the myringotomy ear showing a greater change in hearing (difference from baseline: 16.9 vs. 10.2 dB, p<0.001). Bilateral hearing continued to improve at each subsequent follow-up exam; however, no significant differences were seen between the treatment groups at 3, 7, or 25 years.

Otorrhea

Four trials assessed otorrhea in patients randomized to TT+Ad or myringotomy+Ad: Gates[48,49] (mean age at enrollment not reported, age range 4-8 years, CoE II), Casselbrant 2009[24] (mean age 2.9 years at enrollment, CoE III), Popova[125] (mean age 5.1 years at enrollment, CoE III), Vlastos[169] (sleep apnea patients, mean age 4.5 years at enrollment, CoE III). One RCT assessed outcomes by ear: Shishegar[152] (mean age at enrollment not reported, age range 4-8 years, CoE III); two nonrandomized studies also reported this outcome by ear: Tos/Bonding/Khodaverdi[16,74,160,161] (mean age 3.9 years at enrollment, CoE III) and Caye-Thomasen[26] (mean age 3.9 years at enrollment, CoE III). Overall, results suggest that otorrhea is associated with tubes compared with myringotomy in adenoidectomy patients.

By-child analysis

Otorrhea was 13% to 40% more common in those randomized to TT+Ad than those in the myringotomy+Ad group as measured through 12 months (40% vs. 0%, RD 40%, p<0.001) (Popova[125]), through 18 months (41% vs. 9%, RD 32%, 95% CI 8% to 56%, p=0.0160) (Casselbrant 2009[24]), and through 24 months (24% vs. 11%, RD 13.2%, 95% CI 4.0% to 22.4%, p=0.0053) (Gates[48,49]). When measured through 36 months, the difference between groups was large but did achieve statistical significance in one small trial (47% vs. 18%, RD 30%, 95% CI 1% to 59%, p=0.0626) (Casselbrant 2009[24]). The trial of sleep apnea patients reported no instances of otorrhea in the TT+Ad-Tons patients through 12 months; no data for the control group were reported (Vlastos[169]) (Appendix Table G30).

By-ear analysis

Otorrhea was associated with TT through 6 months in one small trial of adenoidectomy patients (27% TT ears vs. 7% myringotomy ears, RD 20%, 95% CI 2% to 38%, p=0.0393) (Shishegar[152]) (Appendix Table G31). The prospective cohort study reported that 15% of TT ears developed short-term otorrhea during the period in which the tube was functioning; no data were reported for the myringotomy ear

(Tos/Bonding/Khodaverdi[16,74,160,161]). Caye-Thomasen[26] reported that 15% of TT ears had otorrhea while the tube was in place; no data were reported for the myringotomy ear.

AOM

Three trials reported AOM in patients randomized to TT+Ad or myringotomy+Ad: Gates[48,49] (mean age at enrollment not reported, age range 4-8 years, CoE II), Casselbrant 2009[24] (mean age 2.9 years at enrollment, CoE III), and Popova[125] (mean age 5.1 years at enrollment, CoE III). One RCT assessed outcomes by ear: Ruckley[142] (mean age 5.1 years at enrollment, CoE II). In addition, all three nonrandomized cohort nonrandomized studies reported the incidence of AOM by ear: Tos/Bonding/Khodaverdi[16,74,160,161] (mean age 3.9 years at enrollment, CoE III), Leek[81] (mean age at enrollment not reported, age range 2-15 but 95% were age 3-9 years, CoE III), and Caye-Thomasen[26] (mean age 3.9 years at enrollment, CoE III). Overall, the results suggest no difference between groups.

By-child analysis

The incidence of AOM was similar (risk difference: 0-4%, p=NS) between TT+Ad and myringotomy+Ad patients when measured through 12 (Popova[125]), 18 (Casselbrant 2009[24]), 24 (Gates[48,49]), and 36 months (Casselbrant 2009[24]) (Appendix Table G32). One trial reported no difference in the percentage of time spent with AOM through 24 months between groups (risk difference: 0.3%) (Gates[48,49]).

By-ear analysis

Through 3 months, one trial reported that 3% of myringotomy ears developed AOM but did not report data for the tubed ear (Ruckley[142]). One cohort study reported a similar incidence of AOM following tube extrusion in the TT versus myringotomy ears of adenoidectomy patients (risk difference -1%) (Tos/Bonding/Khodaverdi[16,74,160,161]) (Appendix Table G33). Another cohort study reported that 6% of tube ears developed AOM through 19 months, but no data were reported for the myringotomy ear (Leek[81]). Caye-Thomasen[26] reported that after TT extrusion, AOM occurred similarly in TT and myringotomy ears (14% vs. 15%).

AOM or OME

Two trials assessed the percentage of time spent with either OME or AOM in patients randomized to TT+Ad or myringotomy+Ad: Gates[48,49] (mean age at enrollment not reported, age range 4-8 years, CoE II) and Casselbrant 2009[24] (mean age 2.9 years at enrollment, CoE III). While one trial reported that TT+Ad patients spent significantly less time with AOM or OME than myringotomy+Ad patients through 18 months (risk difference, -18%, p=0.0030) and 36 months (risk difference -11%, p=0.0311) (Casselbrant 2009[24]), another trial reported no difference between groups through 24 months (risk difference -4.4%, p=0.1315) (Gates[48,49]) (Appendix Table G34).

OME

Two trials assessed the percentage of time spent with either OME or AOM in patients randomized to TT+Ad or myringotomy+Ad: Gates[48,49] (mean age at enrollment not reported, age range 4-8 years, CoE II) and Popova[125] (mean age 5.1 years at enrollment, CoE III). One RCT and one prospective cohort study assessed outcomes by ear: Ruckley[142] (mean age 5.1 years at enrollment, CoE II) and Leek[81] (mean age at enrollment not reported, age range 2-15 but 95% were age 3-9 years, CoE III). Overall, results suggest that there is either no difference between groups or a slight benefit with TT plus adenoidectomy compared with myringotomy plus adenoidectomy.

By-child analysis
There was no difference in the incidence of OME between groups through 12 or 24 months as reported by one trial each (risk difference: -4% to 0.1%, p=NS) (Popova[125], Gates[48,49]); one trial found that through 24 months, the TT+Ad group spent 5.2% less time with OME compared with the myringotomy+Ad group, however the difference did not reach statistical significance (23.9% vs. 29.1% of time, risk difference -5.2%, 95% CI -10.8% to 0.4%, p=0.0682) (Gates[48,49]) (Appendix Table G35).

By-ear analysis
In one RCT, 19% of myringotomy ears developed OME through 3 months; however, no data were reported for the tubed ears (Ruckley[142]). The prospective cohort study reported that OME was significantly less common in the TT ear compared with the myringotomy ear of adenoidectomy patients through a mean of 19 months (10% vs. 26%, p=0.0096) (Leek[81]) (Appendix Table G36).

Balance and coordination
This outcome was reported in any of the included comparative studies.

Cholesteatoma
One trial (Gates[48,49]) reported that no cholesteatomas formed in either group through 24 months. One prospective cohort study reported similar results between 12 and 36 months in a by-ear analysis (Tos/Bonding/Khodaverdi[16,74,160,161]); one retrospective cohort study found no cholesteatoma in either ear (Caye-Thomasen[26]) when assessed at 3, 7, and 25 years follow-up. Another nonrandomized study reported no instances of cholesteatoma in the TT+Ad-Tons ear; no data were reported for the control ear (Leek[81]).

Functional and quality of life outcomes

Attention and behavioral outcomes, Academic achievement, Speech and language development
None of these outcomes were reported in any of the included comparative studies.

Auditory processing
There was no difference between TT and myringotomy ears in adenoidectomy patients at 6 months in one RCT (Shishegar[152]) (Appendix Table G38).

Parent satisfaction, Patient satisfaction
Neither of these outcomes were reported in any of the included comparative studies.

Patient quality of life
One small trial (N=52) of sleep apnea patients with bilateral OME (Vlastos[169], mean age 4.5 years at enrollment, CoE III) evaluated disease-specific quality of life in patients randomized to TT+Ad-Tons or myringotomy+Ad-Tons. Although there were no differences in mean OM-6 scores (range, 1-7, lower scores indicate better quality of life) between groups at baseline (2.2 vs. 2.0, p=NS), 6 months (1.88 vs. 2.04, p=NS), or 12 months (1.84 vs. 2.04, p=NS), the change from baseline was significantly better at 6 months (-0.38 vs. 0.00, MD -0.38, 95% CI -0.64 to -0.12, p=0.0050). The significance of this result is likely due to the small difference between groups at baseline, with slightly worse scores in the TT+Ad group, compounded with the small difference between groups at 6 months, with slightly better scores in the TT+Ad group. At 12 months, the difference from baseline was slightly smaller between groups and did not achieve statistical significance (-0.32 vs. 0.01, MD -0.33, 95% CI -0.75 to 0.09, p=0.1230) (Appendix Table G39).

Pain

One small trial reported that 3% of myringotomy ears had mild otalgia through 3 months; no data were reported for the tube ears (Ruckley[142]) (Appendix Table G40).

Healthcare utilization

Surgery

(Re)insertion of TT

Two trials reported no significant difference in the (re)insertion of tubes between TT+Ad and myringotomy+Ad patients, with results reported through 18 months (10% vs. 24%, RD -14%, 95% CI -32% to 3%, p=0.1259) (Casselbrant 2009[24]), 24 months (4% vs. 2%, RD 2%, 95% CI -4% to 8%, p=NS) (To[158]), or 36 months (29% vs. 24%, RD 5%, 95% CI -17% to 26%, p=NS) (Casselbrant 2009[24]). While one prospective cohort study (Leek[81]) similarly found no difference between TT and myringotomy ears in adenoidectomy patients who underwent bilateral TT insertion (15% vs. 21%, p=NS), another prospective cohort study (Tos/Bonding/Khodaverdi[16,74,160,161]) reported that 14% myringotomy ears underwent TT insertion during the period of time in which the grommet was still functioning in the contralateral ear (0% vs. 14%, p<0.001). By 12 to 36 months follow-up, the latter study found no difference in the need for tube insertion between TT and myringotomy ears (10% vs. 9%, p=NS) (Appendix Table G41).

Tonsillectomy

Casselbrant 2009[24]) reported that a similar proportion of TT+Ad and myringotomy+Ad patients underwent tonsillectomy through 36 months (13% vs. 6%, RD 7%, 95% CI -7% to 21%, p=NS) (Appendix Table G41).

Surgical retreatment (details not reported)

Gates[48,49]) reported a similar incidence of surgical retreatment (which was typically done using the allocated procedure) between groups (11.2% vs. 11.5%, p=NS) (Appendix Table G41).

Medication usage

Medication usage was reported in one trial that randomized patients to TT+Ad versus myringotomy+Ad: Gates[48,49] (mean age at enrollment not reported, age range 4-8 years, CoE II). Through 24 months, medical retreatment for recurrent OME was similar between groups. However, despite the data that showed no difference in the incidence or frequency of AOM between TT+Ad and myringotomy+Ad patients, medical treatment for AOM was needed in significantly more TT+Ad patients compared with myringotomy+Ad patients (55.2% versus 37.7%, RD 17.5%, 95% CI 55% to 29.6%, p=0.0051); similarly, the TT+Ad group received significantly more medical retreatments for AOM than the myringotomy+Ad group (1.03 vs. 0.66 AOM treatments per child, MD 0.37, 95% CI 0.09 to 0.65, p=0.0091) (Appendix Table G42). Another trial reported that oral antibiotics were needed for 3% of myringotomy ears through 3 months; the need for treatment for the tube ear was not reported (Ruckley[142]) (Appendix Table G43).

Number of office visits

One trial (Gates[48,49]) found that the TT+Ad group had significantly more office visits for illness through 24 months compared with those in the myringotomy+Ad group (0.7 vs. 0.4, MD 0.3, 95% CI 0.1 to 0.5, p=0.0085). Similarly, significantly more TT+Ad patients had office visits for illness compared with those in the myringotomy+Ad group (44.0% vs. 27.7%, RD 16.3%, 95% CI 4.7% to 27.9%, p=0.0067) (Appendix Table G44).

4.1.6. OME: Tubes + Adenoidectomy vs. Adenoidectomy

Studies included

Four RCTs reported across seven publications[14,19,38,91-94] were identified for inclusion. One prospective cohort study[6,7] also met the inclusion criteria. For this comparison, studies which compared tympanostomy tube (TT) insertion plus adenoidectomy to adenoidectomy alone (no treatment in the ear) were sought. All included studies randomized patients by ear; all patients underwent adenoidectomy.

Study characteristics

The included trials were published between the years 1978 and 1994 and sample sizes ranged from 60 to 228 children. All patients underwent adenoidectomy and were further randomized by ear to receive a TT in one ear and no treatment in the other ear. Only two trials reported mean patient age, 6.1 years (Black[14]) and 5.9 years (Dempster[38]); in the other two trials, ages ranged from 4 to 10 years (Brown[19]) and from 2 to 9 years (Maw and Bawden[91-94]). Females comprised 42% to 54% of the population across three trials; the fourth did not provided information on patient sex (Brown[19]). All trials included only patients with bilateral OME; two required OME duration to be three months or longer (Dempster[38], Maw and Bawden[91-94]) and the other two trials did not require a specific OME duration. Hearing loss was required in two trials (Dempster[38], Maw and Bawden[91-94]); the other two trials did not require hearing loss but mean baseline hearing levels suggested that patients had hearing loss. No trials required any additional symptoms for inclusion. The one prospective cohort study included 31 children with bilateral OME (duration not reported) treated in a similar fashion to those in the trials (Austin 1989, 1994[6,7]); however, no information on patient age or sex was provided. Hearing loss was not required for inclusion but was suggested based on overall mean baseline hearing levels. Study characteristics, including quality assessment ratings, are summarized in Table 15.

Intervention details are summarized in Table 16. Briefly, patients underwent surgery with general anesthesia. One trial (Black[14]) and the prospective cohort study (Austin[6,7]) did not specify the use of general anesthesia, however, there was no indication otherwise. Patients received a tube in one ear and did not have any treatment in the contralateral ear. One trial (Maw and Bawden[91-94]) noted that 37% of patients underwent simultaneous tonsillectomy; results were not reported separately for these patient since tonsillectomy was shown to have no added benefit compared with adenoidectomy alone in early cases. All patents in the cohort study also received tonsillectomy but no other details were reported. Tube reinsertion was required in one trial (Maw and Bawden[91-94]) if there was fluid in the ear after tube extrusion and fluid still present in the unoperated ear when there was subjective and objective hearing loss. Tube reinsertion was avoided if at all possible in one trial (Black[14]), not permitted in another trial (Dempster[38]), and not reported in one trial (Brown[19]) or in the prospective cohort study (Austin[6,7]). Reinsertion rates are reported in Table 16.

Table 15. Study characteristics and patient demographics: TT plus adenoidectomy vs. Adenoidectomy for OME

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
TT + adenoidectomy versus Adenoidectomy: randomized by patient										
(none)										
TT + adenoidectomy versus Adenoidectomy: randomized by ear										
Black 1990[14]	149	• Ad + unilateral TT, contralateral no treatment (n=38) • (Ad + unilateral TT, contralateral myringotomy n=37) • (Unilateral TT, contralateral myringotomy, n=37) • (Unilateral TT, contralateral no treatment, n=37)	Bilateral (duration NR)	Not required (mean hearing level at baseline: 28.5 dB)	-	4 – 9 yrs. (6.1 yrs.)	48%	-	1.75 mos. (% NR) 6 mos. (% NR) 12 mos. (85%) 24 mos. (61%)	CoE II
Brown 1978[19]	60	• Ad + unilateral TT, contralateral no treatment (n=60)	Bilateral (duration NR)	Not required (mean hearing level at baseline: 24 dB)	-	4 – 10 yrs. (NR)	NR	-	12 mos. (92%) 60 mos. (92%)	CoE III
Dempster	78	• Ad +	Bilateral	Hearing loss	-	4 – 9 yrs.	54%	-	6 mos. (92%)	CoE III

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
1993[38]		unilateral TT, contralateral no treatment (n=37*) • (Unilateral TT, contralateral no treatment, n=35*)	(≥3 months)	required (≥25 dB) for ≥3 mos.		(5.9 yrs.*)			12 mos. (92%)	
Maw and Bawden 1993, 1994 (4 papers)[91-94]	228	• Ad or Ad/Tons + unilateral TT, contralateral no treatment (n=141) • (Unilateral TT, contralateral no treatment, n=87)	Bilateral (≥3 months)	Hearing loss required (≥25 dB for ≥3 months)	-	2 – 9 yrs. (mean NR)	42%*	-	6 mos. (79%) 12 mos. (97%) 24 mos. (75%) 36 mos. (84%) 48 mos. (74%) 60 mos. (70%) 84 mos. (48%) 120 mos. (30%)	CoE II
Cohort Studies										
Austin 1989, 1994[6,7]	31	• Ad/Tons + unilateral TT, contralateral no treatment (n=31)	Bilateral (duration NR)	Not required (mean hearing level† at baseline: 28 dB)	-	NR (children)	NR	-	1.6-1.9 mos.	CoE III

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

*Data reported only for those with complete follow-up

†bone-air gap

Table 16. Intervention details: TT plus adenoidectomy vs. Adenoidectomy for OME

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Black[14]	Ad + TT (38 ears)	• Anesthesia NR • Unilateral tube (type NR) • Adenoidectomy	• At discretion of treating otolaryngologist, who were asked by investigators to avoid surgical treatment whenever possible	• NR
	Ad (38 ears)	• Anesthesia NR • Adenoidectomy	• Same	• NR
Brown[19]	Ad + TT (60 ears)	• General anesthesia • Unilateral Shepard tube • Adenoidectomy	• NR	• NR
	Ad (60 ears)	• General anesthesia • Adenoidectomy	• NR	• NR
Dempster[38]	Ad + TT (37 ears*)	• General anesthesia • Unilateral Shah tube • Adenoidectomy	• Not permitted	• 0% •
	Ad (37 ears*)	• General anesthesia • Adenoidectomy	• Not permitted	• 0%
Maw and Bawden[91-94]	Ad or Ad/Tons + TT (141 ears)	• General anesthesia • Unilateral Shepard or Goode tube • Adenoidectomy (n=87*) or Adenotonsillectomy (n=52*)	• Reinsertion required if there was fluid in ear after tube extrusion and fluid still present in the unoperated ear when there was subjective and objective hearing loss	• ≤12 months: ~9% • ≤24 months: ~30% • ≤36 months: 33% • ≤48 months: ~33% • ≤60 months: 33.8%
	Ad or Ad/Tons (141 ears)	• General anesthesia • Adenoidectomy (n=87*) or Adenotonsillectomy (n=52*)	• NR	• NR
Cohort Studies				
Austin[6,7]	Ad/Tons + TT (31 ears)	• Anesthesia NR • Unilateral flared polyethylene	• NR	• NR

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
		tube • Adenotonsillectomy		
	Ad/Tons (31 ears)	• Anesthesia NR • Adenotonsillectomy	• NR	• NR

F/U: follow-up; NR: not reported; pop.: population

*Data reported only for those with complete follow-up

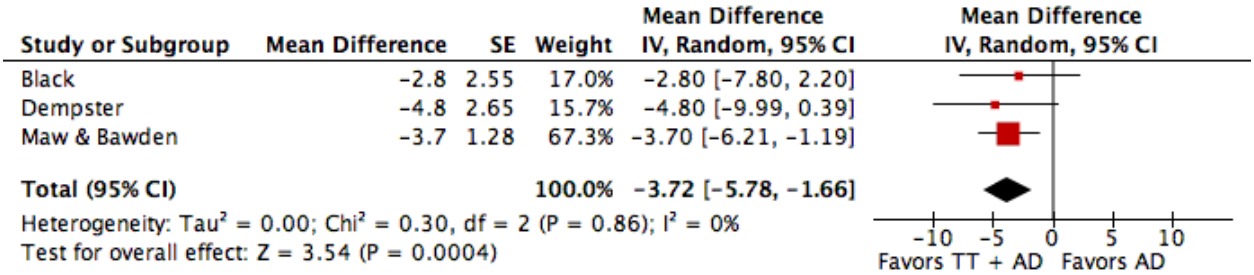
Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G45-G48).

Clinical outcomes

Hearing
All four RCTs reported hearing by ear: Black[14] (mean age 6.1 years at enrollment, CoE II), Brown[19] (mean age NR, age range 4 to 10 years at enrollment, CoE III), Dempster[38] (mean age 5.9 years at enrollment, CoE III), and Maw and Bawden[91-94] (mean age NR, age range 2 to 9 years at enrollment, CoE II). In addition, the prospective cohort study reported hearing levels: Austin[6,7] (mean age, age range NR, CoE III). Detailed results are available in Appendix Table G45.

At 1.6 months, the prospective cohort study reported no difference between groups in air bone gap hearing levels between TT and no treatment ears (13.2 vs. 14.4 dB) (Austin[6,7]). At 3 months, one trial (Brown[19]) found that hearing levels were 5.2 dB lower in TT ears than untreated ears in adenoidectomy patients (11.4 vs. 16.6 dB, p-value not reported). At six months, pooled results from three trials suggest that hearing levels are 3.72 dB better in the TT ear compared with the untreated ear in adenoidectomy patients (MD -3.72 dB, 95% CI -5.78 to -1.66 dB, p=0.0004, I^2=0%) (Figure 19) (Black[14], Dempster[38], Maw and Bawden[91-94]). A fourth trial (which couldn't be pooled due to data limitations) reported that hearing levels were ~2.3 dB lower in the TT ear (16.7 vs. ~19 dB) (Brown[19]). Dempster[38] also reported significantly better air bone gap hearing levels in the ears randomized to TT at 6 months (14.5 vs. 20.4 dB, MD -5.9 dB, 95% CI -10.5 to -1.3 dB, p=0.0136).

Figure 19. Hearing levels by ear at 6 months: TT (unilateral) + Adenoidectomy vs. no treatment (contralateral) + Adenoidectomy for OME



By 12 months, pooled mean differences were no longer statistically significant, with hearing levels 1.36 dB better in the TT ear (MD -1.36, 95% CI -3.17, 0.45, p=0.14, I^2=0%) across three trials (Black[14], Dempster[38], Maw and Bawden[91-94]) (Figure 20); the fourth trial similarly found a mean difference between ears of ~1.0 dB (13.9 vs. ~14.9 dB) (Brown[19]). Dempster[38] also reported no difference between ears in air bone gap hearing levels at 12 months (16.5 vs. 17.2 dB). Results were also statistically similar between ears at 24 months, with a pooled mean difference of -1.93 (95% CI -4.51 to 0.56, p=0.13, I^2=0%) from two trials (Black[14], Maw and Bawden[91-94]) (Figure 21).

Figure 20. Hearing levels by ear at 12 months: TT (unilateral) + Adenoidectomy vs. no treatment (contralateral) + Adenoidectomy for OME

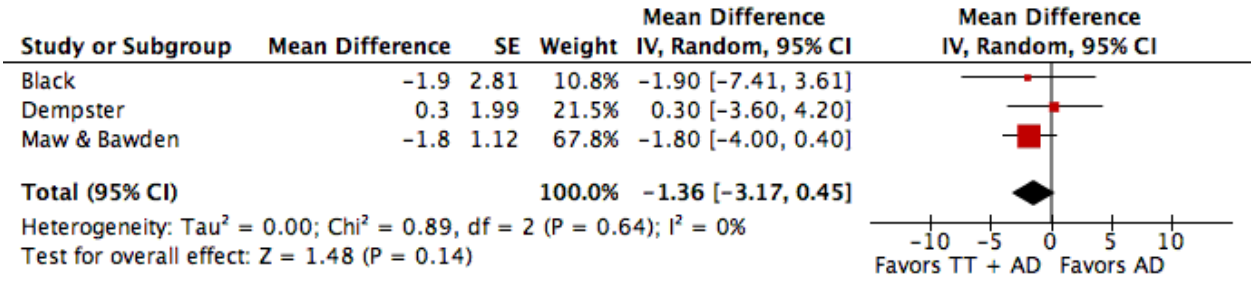
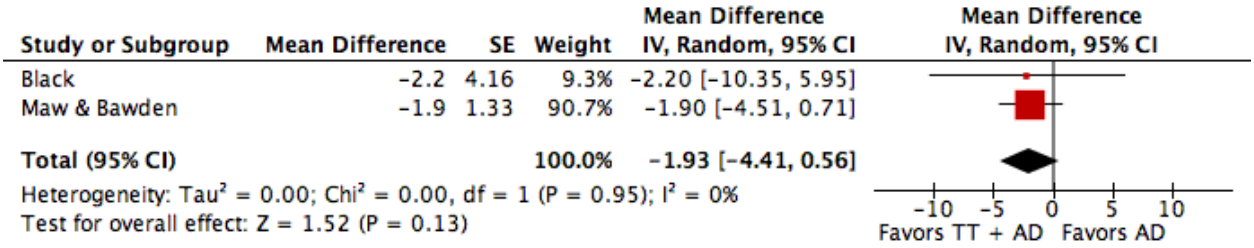


Figure 21. Hearing levels by ear at 12 months: TT (unilateral) + Adenoidectomy vs. no treatment (contralateral) + Adenoidectomy for OME



One RCT found no difference between ears randomized to TT+Ad versus no treatment+Ad at 36 months (MD 0.3 dB), 48 months (MD 0.9 dB), 60 months (MD -0.6 dB), 84 months (MD 1.1 dB), or 120 months (MD 0.1 dB) (Maw and Bawden[91-94]). Another trial reported hearing levels of 17 dB in the TT ear and 14 dB in the untreated ear at 60 months, but the significance of this result was not reported.

OME recurrence

Three trials reported OME recurrence by ear: Brown[19] (mean age NR, age range 4 to 10 years at enrollment, CoE III), Dempster[38] (mean age 5.9 years at enrollment, CoE III), and Maw and Bawden[91-94] (mean age NR, age range 2 to 9 years at enrollment, CoE II). In addition, the prospective cohort study reported OME recurrence: Austin[6,7] (mean age, age range NR, CoE III). Detailed results are available in Appendix Table G46.

Pooled results from two trials (Maw and Bawden[91-94], Dempster[38]) suggest that OME recurrence (as evaluated by otoscopy) occurs in significantly fewer TT ears compared with untreated ears in adenoidectomy patients at both 6 months (pooled RD -38%, 95% CI -48% to -29%, p<0.00001, I^2=0%) (Figure 22) and 12 months (pooled RD -19%, 95% CI -28% to -9%, p=0.0001, I^2=0%) (Figure 23). One of these trials (Maw and Bawden[91-94]) also reported that OME recurrence was less common in the TT ear versus the untreated ear in myringotomy patients at most 24 months (RD -11.6%, 95% CI -23.5% to 0.2%), 36 months (RD -10%, 95% CI -19.0% to -1.0%), 60 months (-10%, 95% CI -19% to -1%), and 120 months (RD -14%, -26% to -1%). The results at 48 and 84 months, however, did not reach (or approach) statistical significance (Appendix Table G46). One RCT reported less OME recurrence (by tympanometry) in the TT ears at 6 months (RD -38%, 95% CI -58% to -17%, p=0.0010) but no difference by 12 months (RD 3%, 95% CI -20% to 35%, p=NS) (Dempster[38]); another trial reported no difference in OME recurrence (by tympanometry) at the 60 month follow-up between ears (RD -2%, 95% CI -8% to 4%)

(Brown[19]). The prospective cohort study found no difference in OME recurrence between TT and untreated ears at 1.9 months (Appendix Table G47).

Figure 22. OME recurrence by ear at 6 months: TT (unilateral) + Adenoidectomy vs. no treatment (contralateral) + Adenoidectomy for OME

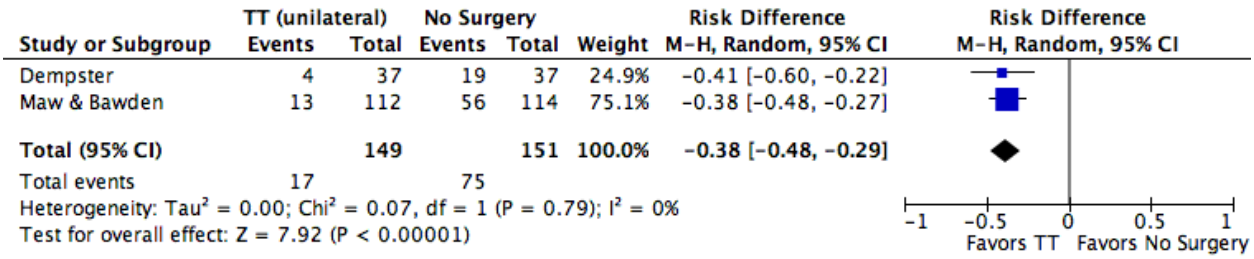
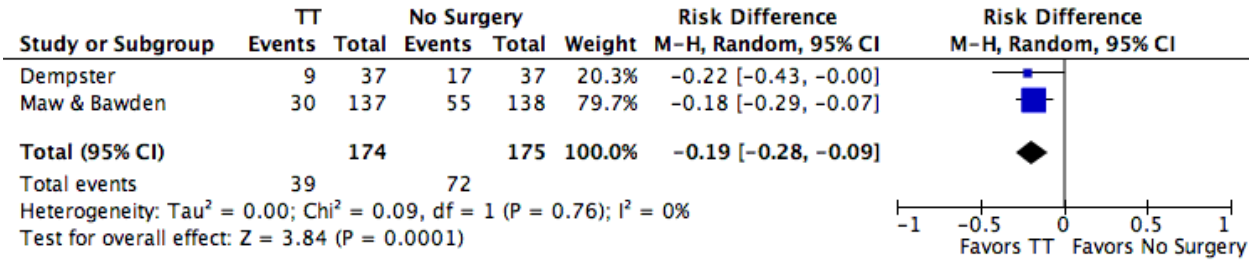


Figure 23. OME recurrence by ear at 12 months: TT (unilateral) + Adenoidectomy vs. no treatment (contralateral) + Adenoidectomy for OME



Cholesteatoma

One trial (Brown[19]) reported no cases of cholesteatoma in either year at the five-year follow-up visit (Appendix Table G47).

Otorrhea, AOM episodes, Balance and coordination

None of the included comparative studies reported these clinical outcomes.

Functional and quality of life outcomes

None of the included studies reported any functional or quality of life outcomes, including attention and behavioral outcomes, academic achievement, speech and language development, auditory processing, patient quality of life, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, or pain.

Healthcare utilization

Surgery

Tube (re)insertion was reported by two trials: Maw and Bawden[91-94] (age range 2 to 9 years at enrollment, CoE II), and Dempster[38] (mean age 5.9 years at enrollment, CoE III). Data are available in table format in Table 16.

The Maw and Bawden[91-94] trial required that reinsertion take place if there was fluid in the ear after tube extrusion in patients who had fluid in the unoperated ear and who had subjective and audiometric hearing loss. During the first year, approximately 9% of TT ears underwent tube reinsertion. By 24

months, 30% of patients underwent reinsertion; after this point, by 60 months, 34% of TT ears had undergone reinsertion. In contrast, Dempster[38] did not permit tube (re)insertion, thus 0% of ears in both groups underwent tube (re)insertion.

Medication usage, Number of office visits
None of the included comparative studies reported these healthcare utilization outcomes.

4.1.7. OME: Tubes versus Myringotomy + Adenoidectomy

Studies included
Two trials compared bilateral tubes alone (no adenoidectomy) to bilateral myringotomy with adenoidectomy: Casselbrant 2009[24] and Gates 1987, 1989[48,49]. Both trials compared patients rather than ears. No nonrandomized cohort studies were identified that met the inclusion criteria.

Study characteristics
The included trials were published between 1987 and 2009 and enrolled 99 and 578 patients. Patient age ranged from 2 to 4 (mean 2.9) years in one trial (Casselbrant[12]) and from 4 to 8 years (mean age not reported) in the second trial (Gates[26, 27]); 66% and 41% of patients were female, respectively. Casselbrant[12] enrolled patients with either bilateral OME (duration ≥3 months) or unilateral OME (duration ≥6 months) and Gates[26, 27] included chronic bilateral and unilateral OME, as well as patients with no effusion at the time of surgery. In both trials, hearing loss was not required for inclusion and baseline hearing loss was not recorded. No other criteria were required for patient inclusion. Follow-up time points, quality assessment, and study characteristics can be found in Table 17.

Intervention details are summarized in Table 18. All patients underwent general anesthesia. Among patients randomized to receive TT, the laterality of insertion in Casselbrant[12] was not reported, but in Gates[26, 27], all were bilateral. In one study, tube reinsertion was permitted if effusion was persistent and adenoidectomy was recommended to patients who had not received it previously (Casselbrant[12]). In the second study (Gates[26,27]) protocols were repeated if effusion reappeared with hearing loss after medical treatment; adenoidectomy was recommended for those in the TT group and tube insertion for those in the myringotomy/adenoidectomy group if OME persisted despite the second procedure. See Table 18 for further detail on reinsertion rates and criteria.

Table 17. Study characteristics and patient demographics: TT vs. Myringotomy + Adenoidectomy for OME

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
Casselbrant 2009[24]	99	• TT* (n=32) • Myringotomy * + Ad (n=34) • (TT* + Ad, n=32)	Bilateral OME ≥3 months OR unilateral OME ≥6 months (or ≥3 months if one TT extruded and other intact)	Not required (baseline hearing levels NR)	None required (63% had nasal obstruction; 35% had previous TT insertion)	2.0 – 3.9 yrs. (2.9 yrs.)	66%	-	18 mos. (67%) 36 mos. (59%)	CoE III
Gates 1987, 1989[48,49]	578	• Bilateral† TT (n=150) • Myringotomy + Ad (n=151) • (Bilateral† myringotomy n=127) • (Bilateral† TT + Ad, n=150)	Laterality of effusion at surgery: bilateral (66%), unilateral (20%), no effusion (14%)†; (chronic OME; duration not further specified)	Not required (baseline hearing levels NR)	-	4 – 8 yrs. (NR yrs.; 71% of patients in these groups were age 6 – 7 yrs.†)	41%†	-	24 mos. (67%)	CoE II
Cohort Studies										
(none)										

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

*Casselbrant: laterality of TT insertion and myringotomy NR

†Demographics reported after exclusion of patients enrolled but did not undergo surgery: Gates: 14% of patients (42/301)

Table 18. Intervention details: TT vs. Myringotomy + Adenoidectomy for OME

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Casselbrant 2009[24]	TT (n=32)	• General anesthesia • Laterality NR • Teflon Armstrong tubes	• Bilateral effusion for 4 consecutive months or for 6 of previous 12 months; OR unilateral effusion for 6 consecutive months or for 8 of previous 12 months	• ≤18 mos.: 10% (3/32) (TT + Ad) • ≤36 mos.: 25% (8/32) (TT + Ad)
	Myringotomy + Ad (n=34)	• General anesthesia • Bilateral • Myringotomy type NR • Adenoidectomy	• same	• ≤18 mos.: 24% (8/34) • ≤36 mos.: 24% (8/34)
Gates 1987, 1989[48,49]	TT (n=150)	• General anesthesia • Bilateral* • Shepard tubes	• Reinsertion: Persistent effusion and hearing level in better ear ≥20 dB after 12 weeks of antibiotics and decongestants • TT+adenoidectomy performed if fluid re-appeared and persisted after second TT procedure	≤24 months: • Any surgical retreatment*: 24.0% (31/129) • 1 surgical retreatment*: 20% (29/129) • 2 surgical retreatments*: 4% (5/129) • 3 surgical retreatments*: 0% (0/129)
	Myringotomy + Ad (n=151)	• General anesthesia • Myringotomy type NR • Adenoidectomy	• TT: if effusion re-appeared and persisted after second myringotomy procedure • (Second myringotomy performed if there was persistent effusion and hearing level in better ear ≥20 dB after 12 weeks of antibiotics and decongestants)	≤24 months: • Any surgical retreatment*: 11.5% (15/130) • 1 surgical retreatment*: 10.0% (13/130) • 2 surgical retreatments*: 1.5% (2/130) • 3 surgical retreatments*: 0% (0/130)

F/U: follow-up; NR: not reported; pop.: population

*Gates 1987, 1989: most surgical retreatments were done according to the protocol, however patients were able to select an alternative treatment (further details NR)

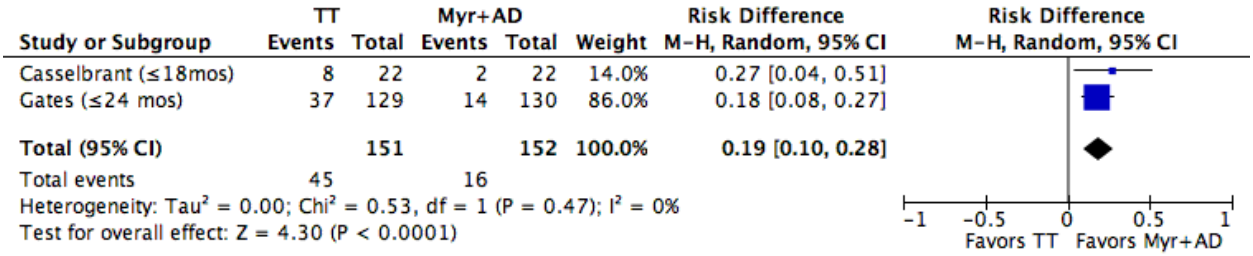
Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G49-G56).

Clinical outcomes

Hearing
Gates[48,49] (mean age NR, range 4-8 years at enrollment) found that there was no difference between groups in the percentage of appointments in which *the better ear* had hearing levels of 20 dB or higher (10.1% vs. 7.8% of appointments, MD 2.3%, 95% CI -9.2% to 5.5%, p=0.1606). However, TT+Ad patients had significantly more appointments with hearing levels *in the worse ear* that were 20 dB or higher (30.4% vs. 22.0% of appointments, MD 8.4%, 95% CI 2.9% to 13.9%, p=0.0028) (Appendix Table G49).

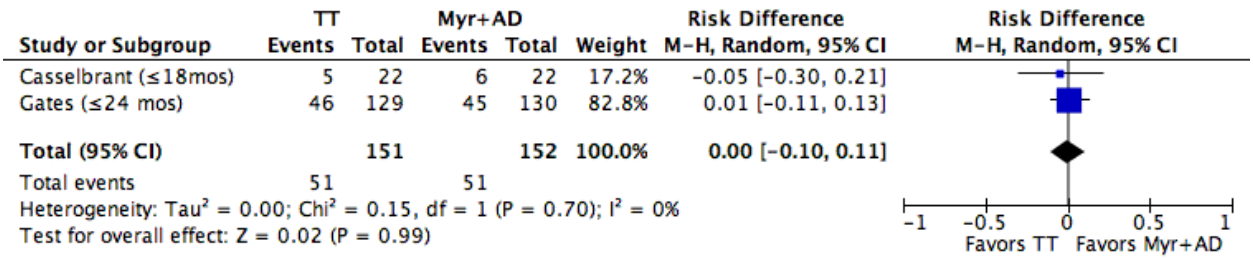
Otorrhea
Pooled results from both trials suggested that otorrhea was significantly more common in the TT group compared with the myringotomy+Ad group as measured through 18 to 24 months (pooled RD 19%, 95% CI 10% to 28%, p<0.0001, I^2=0%) (Figure 24) (Gates[48,49], Casselbrant[24]). One trial found that 27% more TT patients had otorrhea through 36 months (45% vs. 18%), though the result did not reach statistical significance (RD 27%, 95% CI -1% to 56%, p=0.0806) (Appendix Table G50) (Casselbrant[24]).

Figure 24. Otorrhea through 18 to 24 months: TT (bilateral) vs. myringotomy (bilateral) + Adenoidectomy for OME



AOM
Overall, there was no difference between groups in AOM incidence. A similar proportion of patients in each group developed AOM between 18 and 24 months across two trials (pooled RD 0.0%, 95% CI -10% to 11%, p=0.99, I^2=0%) (Figure 25) (Gates[48,49], Casselbrant[24]); similarly, there was no difference between TT and myringotomy+Ad groups through 36 months (55% vs. 53%, p=NS) (Casselbrant[24]). One trial reported no difference been groups in the percentage of time spent with AOM (4.1% vs. 3.6%, p=NS) (Gates[48,49]) (Appendix Table G51).

Figure 25. AOM through 18 to 24 months: TT (bilateral) vs. myringotomy (bilateral) + Adenoidectomy for OME



AOM or OME

Results were inconsistent for the composite outcome of AOM or OME. While Gates[48,49] reported no difference between groups in the percentage of time spent with OME or AOM (34.9% vs. 30.2% of time, p=0.1203), Casselbrant[24] reported that time spent with AOM or OME was significantly lower in the TT group compared with the myringotomy+Ad group through 18 months (12% vs. 36% of time, MD -24%, 95% CI -34% to -13%, p<0.0001) and 36 months (19% vs. 31% of time, MD -13%, MD -22% to -4%, p=0.0076). The 18-month and 24-month data were not pooled across trials due to the high statistical heterogeneity (I^2=96%) that resulted from these large differences.

OME

One trial (Gates[48,49]) reported that a similar proportion of TT and myringotomy+Ad patients had recurrence of OME through 24 months (85.3% vs. 81.5%, p=NS); the percentage of time spend with OME was also no different between groups (31.8% vs. 29.1% of time, p=NS) (Appendix Table G53).

Cholesteatoma

One trial (Gates[48,49]) reported that no cholesteatomas formed in either group.

Balance and coordination

None of the included comparative studies reported this clinical outcome.

Functional and quality of life outcomes

None of the included studies reported any functional or quality of life outcomes, including attention and behavioral outcomes, academic achievement, speech and language development, auditory processing, patient quality of life, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, or pain.

Healthcare utilization

Surgery

Overall, 10% to 25% of TT patients underwent tube reinsertion with or without adenoidectomy, and 0-24% of myringotomy+Ad patients received tubes through 18 to 36 months across two trials (Gates[48,49], Casselbrant[24]) (Appendix Table G54). The indications for tube (re)insertion were different between groups (see Table 18), leading to different surgery rates between trials. Gates[48,49] generally retreated according to the original treatment allocated; through 24 months, 24.0% of TT patients were retreated compared with 11.5% of myringotomy+Ad patients, a difference which was statistically significant (RD 12.5%, 95% CI 3.3% to 21.7%, p=0.0087). Casselbrant[24] reported no statistical difference between groups in the need for TT+adenoidectomy through 18 months (10% vs. 24%, RD -14%, 95% CI -32% to 3%, p=0.1259) or 36 months (25% vs. 24%, p=NS). The same trial also reported similar incidence of myringotomy (3% vs. 0%, p=NS) and tonsillectomy (0% vs. 6%, p=NS) between groups through 36 months.

Medication usage

One RCT (Gates[48,49]) reported medication usage for OME or AOM through 24 months (Appendix Table G55). There was no difference in the percentage of patients needing medical treatment for recurrent OME between groups (84.5% vs. 79.2%, p=NS) or in the mean number of medical retreatments for OME per child (2.6 vs. 2.4, p=NS). More TT patients required medical retreatment for AOM compared with myringotomy+Ad patients, though the difference did not reach statistical significance (48.1% versus 37.7%, RD 10.4%, 95% CI -1.6% to 22., p=0.0.0924); though TT patients required significantly more

medical treatments per child than the TT+Ad group received significantly more medical retreatments for AOM than the myringotomy+Ad group (1.2 vs. 0.7 medical treatments per child, ME 0.6, 95% CI 0.2 to 0.9, p=0.0021).

Number of office visits

One trial (Gates[48,49]) reported that those randomized to TT had 16.5% more office visits for illness through 24 months compared with those randomized to myringotomy+Ad (44.2% vs. 27.7%, RD 16.5%, 95% CI 5.0% to 28.0%, p=0.0058); similarly, the mean number of office visits per child through 24 months was significantly higher in the TT group (0.8 vs. 0.4 visits per child, MD 0.4, 95% CI 0.1 to 0.7, p=0.005) (Appendix Table G56).

4.1.8. OME: Tubes versus Adenoidectomy

Studies included

Two trials compared unilateral tubes alone (no adenoidectomy) to adenoidectomy alone: Dempster[38] and Maw and Bawden[91-94]. The way both trials were designed (patients randomized to adenoidectomy or no adenoidectomy, ears randomized to no treatment or tubes) means that each group has results for one ear only. No nonrandomized cohort studies were identified that met the inclusion criteria.

Study characteristics

The included trials were published between 1993 and 1994; 78 and 228 patients were enrolled. All patients were randomized to receive unilateral TT or unilateral adenoidectomy. Patient age ranged from 4 to 9 (mean 5.9) years in one trial (Dempster[20]) and from 2 to 9 years (mean age not reported) in the other (Maw and Bawden[50-53]); 54% and 42% were female, respectively. The trials enrolled only patients with both bilateral OME and at least 25 dB hearing loss for ≥3 months. Neither trial required additional symptoms for inclusion. Study characteristics including quality assessment ratings are summarized in Table 19.

Intervention details are summarized in Table 20. Briefly, all patients underwent general anesthesia. All TT patients received unilateral placement of the tube and no treatment in the contralateral ear. In one trial (Maw and Bawden[50-53]) some adenoidectomy patients received simultaneous tonsillectomy; results were not reported separately for these patients. Tube reinsertion was not permitted in one trial (Dempster[20]), while the other trial (Maw and Bawden[50-53]) required reinsertion if fluid was still present at time of extrusion and when the unoperated ear experienced fluid presence and subjective or objective hearing loss. Rates of tube reinsertion are reported in Table 20.

Table 19. Study characteristics and patient demographics: TT vs. Adenoidectomy

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
Dempster 1993[38]	78	• TT (one ear only) (N=35) • Ad + no treatment (one ear only) (N=37)	Bilateral (≥3 months)	Hearing loss required (≥25 dB) for ≥3 mos.	-	4 – 9 yrs. (5.9 yrs.*)	54%	-	6 mos. (92%) 12 mos. (92%)	CoE III
Maw and Bawden 1993, 1994 (4 papers)[91-94]	228	• TT (one ear only) (N=87) • Ad or Ad/Tons + no treatment (one ear only) (N=141)	Bilateral (≥3 months)	Hearing loss required (≥25 dB for ≥3 months)	-	2 – 9 yrs. (mean NR)	42%*	-	6 mos. (79%) 12 mos. (97%) 24 mos. (75%) 36 mos. (84%) 48 mos. (74%) 60 mos. (70%) 84 mos. (48%) 120 mos. (30%)	CoE II
Cohort Studies										
(none)										

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

*Demographics reported after exclusion of patients enrolled but did not undergo surgery

Table 20. Intervention details: TT vs. Adenoidectomy

Study	Interventions (n)	Treatment protocol	Indication for tube (re)insertion	Tube (re)insertion (%)
RCTs				
Dempster[38]	TT (one ear only) (N=35)	• General anesthesia • Unilateral • Shah tube	• Not permitted	• 0%
	Ad + no treatment (one ear only) (N=37)	• General anesthesia • Adenoidectomy	• Not permitted	• 0%
Maw and Bawden[91-94]	TT (one ear only) (N=87)	• General anesthesia • Unilateral • Shepard or Goode tube	• Reinsertion required if there was fluid in ear after tube extrusion and fluid still present in the unoperated ear when there was subjective and objective hearing loss	• ≤12 months: 37% • ≤24 months: ~64% • ≤36 months: ~66% • ≤48 months: ~66% • ≤60 months: 68%
	Ad or Ad/Tons + no treatment (one ear only) (N=141)	• General anesthesia • Adenoidectomy (n=87) or Adenotonsillectomy (n=52)	• NR	• NR

F/U: follow-up; NR: not reported; pop.: population

Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G57-G58).

Clinical outcomes

Hearing

Both trials reported hearing by ear: Dempster[38] (mean age 5.9 years at enrollment, CoE III), and Maw and Bawden[91-94] (mean age NR, age range 2 to 9 years at enrollment, CoE II). Detailed results are available in Appendix Table G5.

Hearing levels (by pure-tone audiography) at 6 months were significantly better in the TT ear compared with the no treatment ear in adenoidectomy patients (pooled MD -3.45 dB, 95% CI -6.02 to -0.88 dB, p=0.008, I^2=0%) (Figure 26) (Dempster[38], Maw and Bawden[91-94]). However, one of these trials (Dempster[38]) found no significant difference between groups in air bone gap hearing levels at 6 months (17.3 vs. 20.4 dB, MD -3.1, 95% CI -8.5 to 2.3 dB, p=NS). At 12 months, there was no longer a statistical meaningful difference between groups in mean audiometric hearing levels (pooled MD -0.64 dB, 95% CI -2.86 to 1.58 dB, p=0.57, I^2=0%) (Figure 27); air bone gap hearing levels remained similar between groups (17.9 vs. 17.2 dB, p=NS) in one trial (Dempster[38]).

Figure 26. Hearing levels by ear at 6 months: TT (unilateral) vs. no treatment (contralateral) + Adenoidectomy for OME

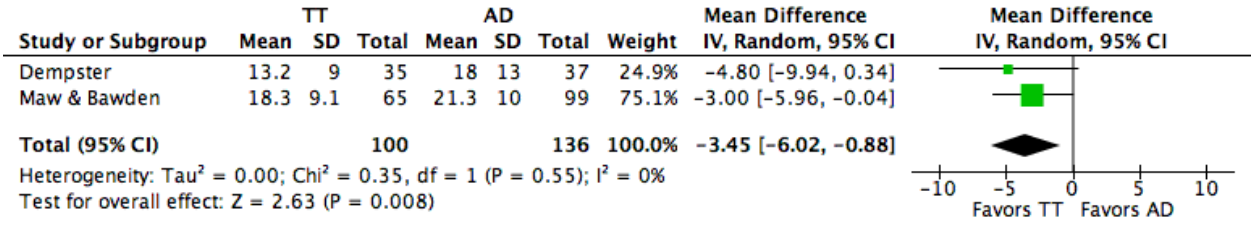
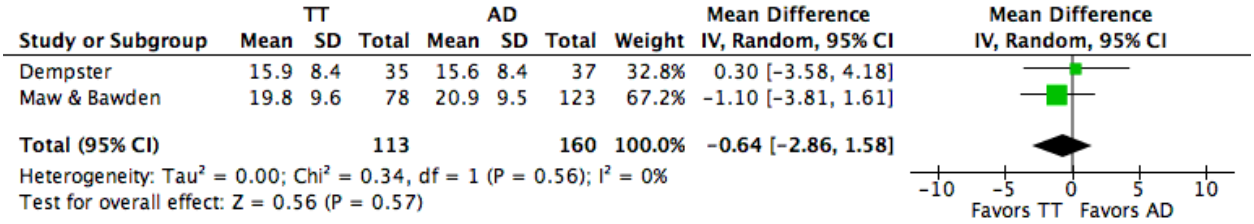


Figure 27. Hearing levels by ear at 12 months: TT (unilateral) vs. no treatment (contralateral) + Adenoidectomy for OME



Maw and Bawden[91-94] also reported hearing levels through ten years follow-up. Although hearing levels were similar between groups at 24 months (20.9 vs. 20.0 dB, p=NS), they were slightly worse in the TT group compared with the Ad group at both 36 months (19.8 vs. 17.0 dB, MD 2.8 dB, 95% CI 0.1 to 5.5 dB, p=0.0428) and 48 months (18.7 vs. 16.6 dB, MD 2.1 dB, 95% CI 0.6 to 3.6 dB, p=0.0066). There were no longer significant differences between the group at 60 months (MD 0.60 dB, 95% CI -2.1 to 3.3 dB), 84 months (MD 0.8 dB, 95% CI -2.6 to 4.2), and 120 months (MD 0.9, 95% CI -2.8 to 4.6) (Appendix Table G58).

OME recurrence

Both RCTs evaluated OME recurrence by ear: Dempster[38] (mean age 5.9 years at enrollment, CoE III) and Maw and Bawden[91-94] (mean age NR, age range 2 to 9 years at enrollment, CoE II). Detailed results are available in Appendix Table G59.

Through 6 months, significantly fewer TT ears had developed OME recurrence compared with untreated ears (in adenoidectomy patients) (pooled MD -34%, 95% CI -44% to -23%, p<0.00001, I^2=0%) (Figure 28) (Dempster[38], Maw and Bawden[91-94]). By 12 months, this difference was no longer statistically significant (pooled MD -6%, 95% CI -17% to 6%, p=0.37, I^2=0%) (Figure 29) (Dempster[38], Maw and Bawden[91-94]).

Figure 28. OME recurrence by ear at 6 months: TT (unilateral) vs. no treatment (contralateral) + Adenoidectomy for OME

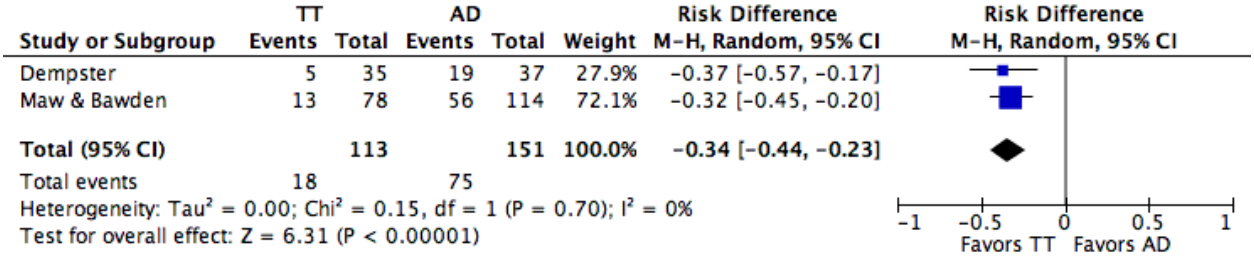
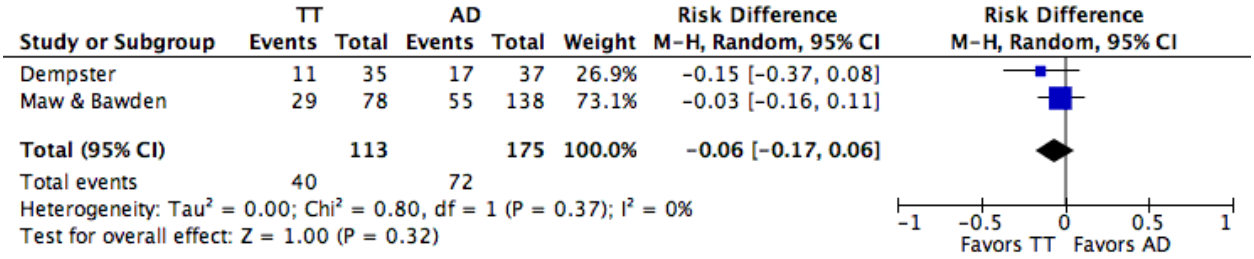


Figure 29. OME recurrence by ear at 12 months: TT (unilateral) vs. no treatment (contralateral) + Adenoidectomy for OME



One trial (Maw and Bawden[91-94]) found no difference between groups in OME recurrence through 36 months (31% vs. 33%), but reported that through 36 months, 15% more ears randomized to TT alone had OME recurrence compared with ears randomized to no treatment (in adenoidectomy patients) (35% vs. 20%, RD 15%, 95% CI 0.5% to 29.3%, p=0.0329). There were no significant differences between groups at any other time point (48, 60, 84, 120 months) (Appendix Table G59).

Cholesteatoma, Otorrhea, AOM episodes, Balance and coordination

Neither trial reported these clinical outcomes.

Functional and quality of life outcomes

None of the included studies reported any functional or quality of life outcomes, including attention and behavioral outcomes, academic achievement, speech and language development, auditory processing, patient quality of life, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, or pain.

Healthcare utilization

Surgery

Tube (re)insertion was reported by two trials: Maw and Bawden[91-94] (age range 2 to 9 years at enrollment, CoE II), and Dempster[38] (mean age 5.9 years at enrollment, CoE III). Data are available in Table 20.

One RCT (Maw and Bawden[91-94]) required that reinsertion occur if there was fluid in the ear after tube extrusion in patients who had fluid in the unoperated ear and who had subjective and audiometric hearing loss. Tube reinsertion during the first year was performed in 37% of TT ears. By the end of the second year, approximately 64% of TT ears underwent reinsertion; by 5 years, 68% of TT ears had undergone reinsertion. No tube insertion data were reported for the control group. The other trial (Dempster[38]) did not permit tube (re)insertion, thus 0% of ears in both groups underwent tube (re)insertion.

Medication usage, Number of office visits

Neither study reported these healthcare utilization outcomes.

4.1.9. OME: Tubes versus Antibiotics

Studies included

One RCT (published in two papers) compared bilateral TT to a 6-month course of antibiotics in patients with bilateral OME and hearing loss for 3 months or longer: Bernard 1991, Stenstrom 2005.[12,154] The study was conducted to determine whether, since middle ear fluid from OME patients commonly contains bacteria, use of antibiotics would be an effective treatment of OME. No nonrandomized cohort studies were identified that met the inclusion criteria.

Study characteristics

The included trial was published across two articles in 1991 and 2005, and included 139 patients randomized to receive bilateral TT or antibiotics (Bernard 1991, Stenstrom 2005[5, 83]). Mean patient age was 4.9 years, 46% were female, and all were required to have both bilateral OME and hearing loss of at least 25 dB for ≥3 months. No additional symptoms were required for inclusion. Study characteristics including quality assessment ratings are summarized in Table 21.

Intervention details are summarized in Table 22. Patients underwent either surgery for bilateral TT placement (use of general anesthesia was not specified, but there was no indication otherwise) or treatment with antibiotics (sulfisoxazole) for 6 months. Tube insertion or reinsertion was indicated upon treatment failure (i.e., persistent/recurrent effusion and hearing loss). Insertion/reinsertion rates can be found in Table 22.

Table 21. Study characteristics and patient demographics: TT vs. Antibiotics for OME

Study	N	Interventions (N)	OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
TT versus Antibiotics for OME: randomized by patient										
Bernard 1991, Stenstrom 2005[12,154]	139	• Bilateral TT (n=68) • Antibiotics (6 months) (n=71)	Bilateral (≥3 months)	Hearing loss required (>3 months, ≥25 dB)	-	2.5 – 7 yrs. (4.9 yrs.*)	46%*	-	2 mos. (90%) 4 mos. (90%) 6 mos. (90%) 12 mos. (90%) 18 mos. (90%) 72-120 mos. (81%)	CoE III
Cohort Studies										
(none)										

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

*Data reported only for those with complete follow-up

†bone-air gap

Table 22. Intervention details: TT plus adenoidectomy vs. Adenoidectomy

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Bernard 1991, Stenstrom 2005[12,154]	TT (n=68)	• Anesthesia NR • Bilateral TT (Reuter in 10/68; Richard "T" in 58/68, which were removed 12-14 mos. after insertion)	• Treatment failure (persistent/recurrent effusion with hearing loss)	• ≤18 mos.: 38% (23/60) • 18-120 mos.: 32% (18/56)
	Antibiotics (n=71)	• Sulfisoxazole (75 mg/kg) divided into two daily doses for 6 months	• Treatment failure (persistent/recurrent effusion with hearing loss) at 6 months	• ≤18 mos.: 48% (31/65) • 18-120 mos.: 53% (30/57)

F/U: follow-up; NR: not reported; pop.: population

*Data reported only for those with complete follow-up

Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G59-G65).

Clinical outcomes

Hearing
All patients had hearing loss of at least 25 dB for three months or longer at baseline (Appendix Table G59). At 2 months, hearing levels were significantly better in the TT group compared with the antibiotics group (~11 vs. ~20 dB, p<0.001; similar results were found at 4 months (~12 vs. ~17 dB, p=0.0132) (Bernard, Stenstrom[12,154]). At both these time points, significantly fewer TT patients had hearing levels greater than 25 dB versus antibiotics patients, although no data were reported. There was no difference in mean hearing levels or the percentage of patients with hearing levels over 25 dB between groups between 6 and 18 months. Between 72 and 120 months follow-up, there was no significant difference between groups as randomized in mean hearing levels (hearing was 2.1 to 4.7 dB higher in TT patients across different frequencies, p=0.15), however slightly more TT patients had hearing levels over 15 dB (RR 1.8, 95% CI 1.1 to 3.1). When analyzed as treated, the 86 patients who received tubes regardless of treatment allocation had significantly higher hearing levels across different frequencies than the 27 patients who never received tubes (5.1 to 10.8 dB higher, p<0.001), similarly, significantly more tubed patients had hearing levels higher than 15 dB (RR 3.8, 95% CI 1.3 to 11.3, p<0.005). This result was upheld even when considering only those who received one tube (n=38) to those who never received a tube (n=27) in terms of hearing levels (MD ~5 dB between groups, p<0.05) and the percentage of patients with hearing levels greater than 15 dB (37% vs. 11%, RD 26%, 95% CI 6% to 45%, p=0.0210).

"Treatment failure"
The composite outcome "treatment failure" (any of the following: (1) persistent/recurrent MEE and associated hearing loss (>25 dB HL at 2 or more frequencies 0.5, 1, 2, and 4 kHz, in at least one ear); (2) allergic reaction to sulfonamide (for medical group only); or (3) three or more AOM episodes over a 6-month period of the study) was met by fewer TT patients compared with antibiotics patients at 6 months (20% vs. 34%, p=0.0834), 12 months (40% vs. 60%, p=0.0261) and 18 months (48% vs. 68%, p=0.0289) (Appendix Table G60) (Bernard, Stenstrom[12,154]).

Otorrhea
Otorrhea through the tube occurred in 13% (8/60) of patients in the TT group through 18 months (Bernard, Stenstrom[12,154]); no data were reported for the antibiotic group.

AOM episodes, OME recurrence, Cholesteatoma Balance and coordination
These outcomes were not reported.

Functional and quality of life outcomes

Academic achievement
Bernard and Stenstrom[12,154] reported that the percentage of patients with parent-reported inadequate school performance was similar between those who received tubes only once (n=38) and those who never received tubes (n=27) (13% vs. 7%, RD 6%, 95% CI -9% to 20%, p=NS) (Appendix Table G61). Data were not reported according to treatment allocation.

Parent satisfaction
When measured between 72 and 120 months post-treatment, parent-reported treatment satisfaction was similar for children who received tubes only once (n=38) versus those who never received tubes (n=27) (92% vs. 81%, RD 11%, 95% CI -6% to 28%, p=NS) (Appendix Table G62) (Bernard, Stenstrom[12,154]). Data were not reported according to treatment allocation.

Pain
The parent-reported composite outcome of pain or decreased hearing was 18% higher in those patients who received tubes once (n=38) compared with those who never received tubes (n=27), although the results did not reach statistical significance (29% vs. 11%, RD 18%, 95% CI -1% to 37%, p=NS) (Appendix Table G63) (Bernard, Stenstrom[12,154]). Data were not reported according to treatment allocation.

Attention and behavioral outcomes, Auditory processing, Speech and language development, Patient quality of life, Patient satisfaction
These outcomes were not reported.

Healthcare utilization

Surgery
While there was no statistical difference between groups in tube (re)insertion through 18 months (38% vs. 48%, RD -9%, 95% CI -27% to 8%, p=NS), significantly fewer TT patients underwent tube (re)insertion through 72-130 months (32% vs. 53%, RD -20%, 95% CI -38% to -3%, p=0.0283) (Appendix Table G64) (Bernard, Stenstrom[12,154]).

Medication usage
Sulfonamide (re)treatment given in a similar percentage of patients in the TT versus antibiotics group through 18 months (10% vs. 20%, MD -10%, 95% CI -22% to 2%, p=0.1212) (Appendix Table G65) (Bernard, Stenstrom[12,154]).

Number of office visits
This outcome was not reported.

4.1.10. AOM: Tubes versus Antibiotics

Studies included
Four RCTs were identified for inclusion[23,43,50,54]. No nonrandomized cohort studies were identified that met the inclusion criteria. Studies comparing TT insertion to medication were sought; all identified studies compared TT insertion to antibiotics.

Study characteristics
The included trials were published between the years 1981 and 1996, and enrolled between 65 and 264 patients. Mean patient age ranged from 1.4 to 1.7 across three trials (El Sayed[23], Gebhart[28], Gonzalez[29]); one trial did not report mean age (Casselbrant[11]). Across the trials, 37% to 41% of patients were female. All trials required patients to have had three or more AOM episodes within 6 months; or, in two of the trials, four or more episodes within 12 months (the last of which was within 6 months) (Casselbrant[11]) or within the past 18 months (Gonzalez[29]). Hearing loss was not required for inclusion and baseline hearing loss was not recorded in any of the trials. Casselbrant[11] required patients to be free of middle ear effusion, however all other trials required no additional symptoms for inclusion. Study characteristics, including quality assessment ratings, are summarized in Table 23.

Intervention details are summarized in Table 24. Patients randomized to receive TT were treated with general anesthesia and bilateral tube placement (Casselbrant[11], Gebhart[28], and Gonzalez[29]), with the exception of one trial in which tube placement was unilateral or bilateral (El Sayed[23]). Those randomized to medical treatment received antibiotics over periods ranging from 10 days to 6 months, and one trial included otic suspension drops if drainage was present (Gebhart[28]). Indications for reinsertion varied and included early extrusion (Gebhart[28], El Sayed[23]), recurrent infection (Gebhart[28]), development of AOM or OME (Casselbrant[11], Gonzalez[29]) and other (see Table 24 for details of reinsertion criteria and rates).

Table 23. Study characteristics and patient demographics: TT vs. Antibiotics for AOM

Study	N	Interventions (N)	AOM	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
Casselbrant 1992[23]	264	• Bilateral TT (n=86) • Antibiotic (n=90) • (Placebo, n=88)	≥3 AOM episodes within 6 mos., or ≥4 AOM episodes within 12 mos. and last episode within 6 mos.	Not required (baseline hearing levels NR)	Free of middle ear effusion	0.6 – 2.9 yrs. (NR)	41%	-	6 mos. (% NR) 12 mos. (% NR) 18 mos. (% NR) 24 mos. (69%)	CoE III
El Sayed 1996[43]	68	• Unilateral or bilateral TT* (n=31†) • Antibiotic (n=22†)	≥3 AOM episodes within 6 mos.	Not required (baseline hearing levels NR)	-	0.75 – 3 yrs. (1.4 yrs.†)	37%†	-	2 mos. (% NR) 4 mos. (% NR) 6 mos. (80%)	CoE III
Gebhart 1981[50]	108	• Bilateral TT (n=58) • Antibiotic (n=50)	≥3 AOM episodes within 6 mos. despite antibiotic therapy	Not required (baseline hearing levels NR)	-	NR – 3 yrs. (1.7 yrs.)	37%	-	6 mos. (88%)	CoE III
Gonzalez 1986[54]	65†	• Bilateral TT (n=22‡) • Antibiotic (n=21‡) • (Placebo, n=20‡)	≥3 AOM episodes within 6 mos., or ≥4 AOM episodes within 18 mos.	Not required (baseline hearing levels NR)	-	0.5 – 4 yrs. (1.5 yrs.)	40%	-	6 mos. (%NR)	CoE II
Cohort Studies										
(none)										

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

*Percentage of patients treated unilaterally or bilaterally was not reported

†Data reported for patients with complete follow-up only

‡Data reported for patients aged 4 and under with complete follow-up

Table 24. Intervention details: TT vs. Antibiotics for AOM

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Casselbrant 1992[23]	**TT (n=86)**	• General anesthesia • Bilateral • Teflon Armstrong tubes	• TT obstructed despite antibiotic treatment and: <6 months since TT insertion, 6-12 since TT insertion and AOM or OME developed, or >12 months since TT insertion and antibiotic and tympanocentesis AOM or OME developed within 6 months of first recurrence or if middle ear effusion persisted for >3 months	• ≤24 mos.: 28%
	Antibiotics (n=90)	• Amoxicillin: 20 mg/kg 1X/day for 4 weeks	• NR	• NR
El Sayed[43]	**TT (n=31†)**	• General anesthesia • Unilateral or bilateral TT* (type NR)	• Early extrusion	• ≤6 mos.: 7%
	Antibiotic (n=22†)	• Combination of sulfamethoxazole and trimethoprim (SMZ-T) syrup, 12 mg/kg 1X per day for 6 months	• NR	• NR
Gebhart[50]	**TT (n=58)**	• General anesthesia • Bilateral Shepard Teflon TT	• Early extrusion or presence of a blood clot in the lumen of the tube and subsequent recurrent infection	• ≤6 mos.: 6% • ≤30 mos.: 37%
	Antibiotic (n=50)	• Ampicillin or erythromycin and a sulfonamide for 10 days, and Cortisporin otic suspension	• NR	• NR

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
		drops if drainage present		
Gonzalez[54]	**TT (n=22†)**	• General anesthesia • Bilateral Parapella TT	• NR	• NR
	Antibiotic (n=21†)	• Sulfisoxazole, 500 mg 2x/day for 6 months	• ≥2 AOM episodes within 3 months, or OME for ≥3 months	• NR‡

F/U: follow-up; NR: not reported; pop.: population

*Percentage of patients treated unilaterally or bilaterally was not reported

†Data reported for patients aged 4 and under with complete follow-up

‡For the antibiotics (n=21) and placebo (n=20) groups combined, 46% (19/41) underwent TT insertion

Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G66-G72).

Clinical outcomes

Hearing
Two trials reported hearing levels: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III) and Gebhart[50] (mean age 1.7 years at enrollment, CoE III). Neither study required hearing loss for enrollment, nor were baseline hearing levels reported.

Through 24 months, one trial (Casselbrant 1992[23]) reported no difference between TT and antibiotics groups in the percentage of time spent with hearing levels above 15 dB (10% vs. 12% of time, p=NS). The other trial (Gebhart[50]) reported one TT patient (2%) presented with moderately severe sensorineural hearing loss at 42 months; due to the patient's family history of this condition, the authors concluded that the hearing loss was not related to the tubes or to the AOM history.

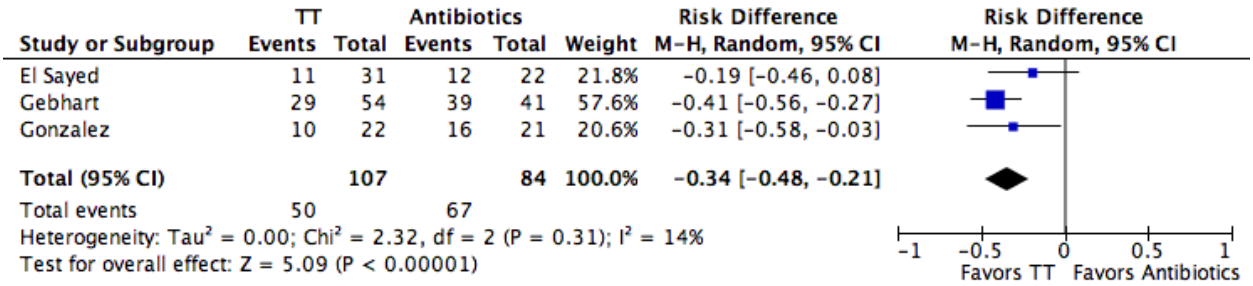
Otorrhea
This outcome was not reported on its own by any of the included studies but was reported with AOM episodes (see below).

Otorrhea or AOM
One RCT reported the composite outcome of otorrhea or AOM: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III). TT patients had 0.42 more new episodes of AOM or otorrhea per year (over two years) than those in the antibiotics group (1.02 vs. 0.60 new episodes per year, p=0.001).

AOM episodes
AOM recurrence was reported by three RCTs: El Sayed[43] (mean age 1.7 years at enrollment, CoE III), Gebhart[50] (mean age 1.7 years at enrollment, CoE III), and Gonzalez[54] (mean age 1.5 years at enrollment, CoE II).

Results could be pooled across all three trials (El Sayed[43], Gebhart[50], Gonzalez[54]), which showed that through 6 months, the TT group was 34% less likely to have a recurrence of AOM compared with the antibiotics group (pooled RD -34%, 95% CI -48% to -21%, p<0.00001, I^2=14%) (Figure 30) (Appendix Table G68). Gonzalez[54] reported no significant difference in the mean number of AOM episodes per child through 6 months (0.9 vs. 1.4).

Figure 30. AOM recurrence through 6 months: TT vs. Antibiotics for AOM



OME episodes
OME occurrences were evaluated by one trial: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III). Through 24 months, Casselbrant 1992[23] found that TT patients had a mean of 0.32 fewer new OME episodes per year compared with antibiotics patients (0.38 vs. 0.70), although the p-value was not reported and could not be calculated.

Cholesteatoma
Two RCTs reported no cholesteatomas through 24 and 30 months: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III) and Gebhart[50] (mean age 1.7 years at enrollment, CoE III), respectively.

Balance and coordination
This outcome was not reported by any of the included studies.

Functional and quality of life outcomes
None of the included studies reported any functional or quality of life outcomes, including attention and behavioral outcomes, academic achievement, speech and language development, auditory processing, patient quality of life, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, or pain.

Healthcare utilization

Surgery
Tube reinsertion was performed in 6% to 7% of TT patients across two trials (Gebhart[50], El Sayed[43]); these trials did not report data for the antibiotics group. A third trial reported that 46% of patients in the antibiotics or placebo group combined (19/41) underwent tube insertion by 6 months (Gonzalez[54]) but reported no data for the TT group. Through 24 months, tube reinsertion was performed in 28% of patients in one trial (Casselbrant 1992[23]), and through 30 months, the procedure was performed in 37% of TT patients (Gebhart[50]); again, no data were reported for the control groups.

Medication usage
Gonzalez[54] (mean age 1.5 years at enrollment, CoE II) reported that 18% of TT patients required chemoprophylaxis for treatment failure by 6 months follow-up.

Number of office visits
This outcome was not reported by any of the included studies.

4.1.11. AOM: Tubes versus Placebo or No Treatment

Studies included
Three RCTs (in four publications) met the inclusion criteria[23,54,77,78]. Two of these trials also included an antibiotics treatment arm and included a placebo group (Casselbrant 1992[23] and Gonzalez[54]), the third trial compared bilateral TT to no treatment (Kujala[77,78]). No nonrandomized cohort studies were identified that met the inclusion criteria.

Study characteristics
The included trials were published between the years 1986 and 2014 and sample sizes ranged from 65 to 264 children. All patients were randomized to either bilateral TT insertion or placebo/no treatment.

Two trials reported mean patient ages of 1.5 years (Gonzalez 1986[54]) and 1.3 years (Kujala 2012, 2014[77,78]) and in the third trial, ages ranged from 0.6 to 2.9 years (Casselbrant 1992[23]); females comprised 41% to 45% of the populations. All trials included only patients with three or more episodes of AOM within the previous 6 months; two studies further included patients with four or more episodes occurring either within the past 12 months (with the last episode within 6 months) in one trial (Casselbrant 1992[23]) or within the past 18 months in the other (Gonzalez 1986[54]). Hearing loss was not required for inclusion and baseline hearing loss was not recorded in any of the trials. Two trials (Casselbrant[11] and Kujala 2012, 2014[77,78]) required patients to be free of middle ear effusion; the third trial required no additional symptoms for inclusion. Study characteristics, including quality assessment ratings, are summarized in Table 25.

Intervention details are summarized in Table 26. Briefly, patients underwent bilateral surgery with general anesthesia. In two trials, the control groups received a placebo identical in appearance to amoxicillin (Casselbrant 1992[23]) and to sulfisoxazole (Gonzalez 1986[54]), and in the third trial patients in this group underwent no treatment (no described further). TT reinsertion was indicated in one trial when the tube was obstructed despite antibiotic treatment and recurrent AOM or OME developed (Casselbrant 1992[23]); the other trials did not report tube reinsertion. Reinsertion rates and further details regarding reinsertion criteria can be found in Table 26.

Table 25. Study characteristics and patient demographics: TT vs. Placebo or No treatment for AOM

Study	N	Interventions (N)	AOM	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
Casselbrant 1992[23]	264	• Bilateral TT (n=86) • Placebo (n=88) • (Antibiotic, n=90)	≥3 AOM episodes within 6 mos., ≥4 AOM episodes within 12 mos. and last episode within 6 mos.	Not required (baseline hearing levels NR)	Free of middle ear effusion	0.6 – 2.9 yrs. (NR)	41%	-	6 mos. (% NR) 12 mos. (% NR) 18 mos. (% NR) 24 mos. (69%)	CoE III
Gonzalez 1986[54]	65†	• Bilateral TT (n=22‡) • Placebo (n=20‡) • (Antibiotic, n=21‡)	≥3 AOM episodes within 6 mos., or ≥4 AOM episodes within 18 mos.	Not required (baseline hearing levels NR)	-	0.5 – 4 yrs. (1.5 yrs.)	40%	-	6 mos. (% NR)	CoE II
Kujala 2012, (Kujala 2014 subanalysis§) [77,78]	300	• Bilateral TT (n=100) • No treatment (n=100) • (Bilateral TT + Ad, n=100)	≥3 AOM episodes within 6 mos.,	Not required (baseline hearing levels NR)	Free of middle ear effusion	0.8 – 2 yrs. (1.3 yrs.)	45%	-	4 mos. (subanalysis, % f/u unclear) 12 mos. (90%)	CoE II
Cohort Studies										
(none)										

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

†Data reported for patients with complete follow-up only

‡Data reported for patients aged 4 and under with complete follow-up

§Kujala 2014 subanalysis: QoL was not evaluated in the first 141 patients included in the RCT; QoL was evaluated in the subsequent 159 consecutive patients in the RCT. In the subanalysis, baseline characteristics remained similar between groups.

Table 26. Intervention details: TT vs. Placebo or No treatment for AOM

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Casselbrant 1992[23]	TT (n=86)	• General anesthesia • Bilateral • Teflon Armstrong tubes	• TT obstructed despite antibiotic treatment and: <6 months since TT insertion, 6-12 since TT insertion and AOM or OME developed, or >12 months since TT insertion and antibiotic and tympanocentesis AOM or OME developed within 6 months of first recurrence or if middle ear effusion persisted for >3 months	• ≤24 mos.: 28%
	Placebo (n=88)	• Placebo (identical in appearance to amoxicillin) 1X/day for 4 weeks	• NR	• NR
Gonzalez[54]	TT (n=22*)	• General anesthesia • Bilateral Parapella TT	• NR	• NR
	Placebo (n=20*)	• Placebo (identical in appearance to sulfisoxazole) 2x/day for 6 months	• ≥2 AOM episodes within 3 months, or OME for ≥3 months	• NR†
Kujala 2012, 2014[77,78]	TT (n=100)	• General anesthesia • Bilateral Donaldson TT	• NR	• NR
	No treatment (n=100)	• NR	• NR	• NR

F/U: follow-up; NR: not reported; pop.: population

*Data reported for patients aged 4 and under with complete follow-up

†For the antibiotics (n=21) and placebo (n=20) groups combined, 46% (19/41) underwent TT insertion

Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G73-G79).

Clinical outcomes

Hearing
Hearing levels were reported in one trial: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III). This study did not require hearing loss for enrollment, nor did it report baseline hearing levels. Through 24 months, TT patients spent 10% of the time with hearing levels above 15 dB in the better ear compared with 16% in the placebo group (Appendix Table G73). The statistical significance of this result was not reported and could not be calculated.

Otorrhea
This outcome was not reported on its own but was reported in conjunction with AOM episodes (see below).

Otorrhea or AOM
Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III) reported that there was no difference in the mean number of new episodes of either otorrhea or AOM per year (over two years) between TT and placebo groups (1.02 vs. 1.08 new episodes per year, p=NS) (Appendix Table G74).

AOM recurrence
AOM recurrence was evaluated by two trials: Gonzalez[54] (mean age 1.5 years at enrollment, CoE II) and Kujala[77,78] (mean age 1.3 years at enrollment, CoE II). Both found that the percentage of patients with AOM recurrence was significantly lower in the TT group compared with the no treatment group, and was measured through 6 months (45% vs. 85%, RD -40%, 95% CI -66% to -14%, p=0.0083) (Gonzalez[54]) and 12 months (52% vs. 66%, RD -14%, 95% CI -14% to -0.5%, p=0.0447) (Kujala[77,78]). Both trials also reported that TT patients had fewer episodes of AOM compared with placebo or no treatment, although the statistical significance was not reported: 0.9 vs. 2.0 episodes over 6 months (Gonzalez[54]), and 1.15 vs. 1.70 over 12 months (Kujala[77,78]) (Appendix Table G75).

OME episodes
Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III) reported that through 24 months, the TT group had, on average, 0.24 fewer new OME episodes per year versus the placebo group (0.38 vs. 0.62), although the p-value was not reported and could not be calculated (Appendix Table G76).

Cholesteatoma
Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III) reported no cases of cholesteatoma in either group through 24 months.

Balance and coordination
This outcome was not reported by any of the included studies.

Functional and quality of life outcomes

Patient quality of life

A subanalysis of one trial (Kujala[77,78] (CoE II) was conducted. During the second half of the trial only, consecutive patients were sent quality of life questionnaires. Of the 100 patients randomized to TT, 53 consecutive patients were evaluated for quality of life; of the 100 patients allocated to no treatment, 52 consecutive patients were sent quality of life questionnaires. The baseline characteristics between the subset of each group appeared to be similar; the mean age across the subgroups was 3.6 years at baseline, and hearing levels at baseline were not reported.

Disease-related quality of life was evaluated at 4 and 12 months follow-up in two ways: using a 10-point VAS scale (higher scores indicate better ear-related quality of life), and using the disease-specific OM-6 (1-7 scale for each subgroup, lower scores indicate better quality of life). There were no differences between treatment groups in either outcome measure at baseline, 4 months, or 12 months. Detailed data are available in Appendix Table G78.

Attention and behavioral outcomes, Academic achievement, Speech and language development, Auditory processing, Parent satisfaction with treatment/outcomes, Patient satisfaction with treatment/outcomes, Pain

None of the included studies reported any other functional or quality of life outcomes.

Healthcare utilization

Surgery

Gonzalez[54] (mean age 1.5 years at enrollment, CoE II) did not report data on tube reinsertion for the TT group; in both the placebo and antibiotics groups combined, 46% of patients (19/41) underwent tube insertion through 6 months. Through 24 months, Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III) reported that 28% of TT patients underwent tube reinsertion but did not report tube insertion data for the control group.

Medication usage, Number of office visits

These outcomes were not reported by any of the included studies.

4.1.12. AOM or OME: Tubes (unilateral) versus Myringotomy or No Treatment (contralateral)

Studies included

One trial enrolled patients with bilateral AOM (72%) or OME (23%) and randomized one ear to TT and the other ear to either myringotomy alone or no treatment (results not stratified between the two comparators): Le 1991[79] (mean age 2.3 years at enrollment, CoE III). No nonrandomized cohort studies were identified that met the inclusion criteria.

Study characteristics

The included trial was published in 1991 and included 57 patients (44% female) with a mean age of 2.3 years (range, 0.8 to 6.8 years). To be eligible for inclusion, the children had to have either bilateral recurrent AOM (≥4 episodes if age <1 year or ≥6 episodes within 12 months if age >1 year) or bilateral OME (≥3 months duration); hearing loss was not required and baseline hearing levels were not reported. No additional symptoms were required for inclusion. Study characteristics including quality assessment ratings are summarized in Table 27.

Intervention details are summarized in Table 28. Patients were randomized by ear to undergo TT placement (with general anesthesia) in one ear and either myringotomy or no treatment in the contralateral ear. Tube insertion or reinsertion was indicated if the patient experienced recurrent AOM or persistent OME (not defined further) over the course of follow-up. Insertion/reinsertion rates can be found in Table 28.

Table 27. Study characteristics and patient demographics: TT (unilateral) vs. Myringotomy or no treatment (contralateral) for AOM or OME

Study	N	Interventions (N)	AOM Or OME	Hearing Loss	Additional Symptoms Required	Age Range (Mean)	Female (%)	Special Pop.	F/U Time Points (%)	Study Quality
RCTs										
Le 1991[79]	57	• Unilateral TT (57 ears) • Unilateral myringotomy or no treatment (57 ears)	AOM (n=44): ≥4 bilateral AOM episodes if age <1 yr.; or ≥6 bilateral AOM episodes within 12 mos. if age ≥1, or OME (n=13): bilateral OME for ≥3 mos.	Not required (baseline hearing levels NR)	-	0.8 – 6.8 yrs. (2.3 yrs.)	44%	-	6 mos. (100%) 12 mos. (100%) 18 mos. (100%) 24 mos. (98%) 36 mos. (98%)	CoE III
Cohort Studies										
(none)										

Ad: adenoidectomy; F/U: follow-up; NR: not reported; pop.: population

Table 28. Intervention details: TT (unilateral) vs. Myringotomy or no treatment (contralateral) for AOM or OME

Study	Interventions (N)	Treatment Protocol	Indication For Tube (Re)Insertion	Tube (Re)Insertion (%)
RCTs				
Le[79]	TT (57 ears)	• General anesthesia • Unilateral Pope Teflon tubes	• Recurrent AOM or persistent OME (not defined	• ≤24 mos.: 5%
	Myringotomy or no treatment (57 ears)	• Myringotomy or no treatment (details NR) • Unilateral	• same	• ≤24 mos.: 7%

F/U: follow-up; NR: not reported; pop.: population

Results:
Detailed results tables for this section are available in Appendix G (Appendix G tables G80-G83).

Clinical outcomes

Hearing
Hearing loss was not required for inclusion, and baseline hearing levels were not reported. Between 3 and 9 months follow-up, hearing levels were 3.4 to 3.7 dB better in the TT ear than the control ear: MD -3.4 dB at 3 months (95% CI -6 to -1 dB, p=0.02), MD -3.7 dB at 6 months (95% CI -7 to 0, p=0.05), MD -3.5 at 9 months (95% CI -6 to 0, p=0.02) (Le[79]). Further, at 9 months, 32% of patients had hearing levels at least 5 dB lower in the TT ear (p=0.04). At 12 and 15 months, hearing levels were similar between ears, with mean differences ranging from -0.8 to 0.2 dB. At 17 months, 28% of patients had better hearing (≥5 dB difference) in the TT ear (p0.013). At 18 months, hearing levels were slightly worse in the TT ear compared with the control ear, with a mean difference of 2.1 dB (95% CI 0 to 4 dB, p=0.08), although the result did not reach statistical significance. At 24 months, 14% of patients had hearing levels that were at least 5 dB better in the TT ear (p=0.36). While there was no difference between ears at 24 months (MD 0.2 dB), after 24 months hearing levels were 1.7 dB better in the control ear (95% CI 0 to 4 dB), but again, the difference was not statistically meaningful (Appendix Table G80).

Otorrhea
While there was no difference between ears in the incidence of otorrhea within the first 2 weeks of surgery (4% vs. 2%), significantly more TT ears had otorrhea than control ears through 2 months (14% vs. 2%, RD 12%, 95% CI 3% to 22%, p=0.0155) and through 3 months (18% vs. 2%, RD 16%, 95% CI 5% to 26%, p=0.0045) (Appendix Table G81) (Le[79]). Three TT ears (5%) had three or more episodes of purulent otorrhea over the 24 month study period.

AOM
The mean number of AOM episodes per 6 months was significantly lower in the TT ear than the control ear as measured between 0 and 6 months (0.5 vs. 1.4 episodes, MD -0.9, 95% CI -1.3 to -0.5, p<0.0001) and between 7 and 12 months (0.6 vs. 1.0 episodes, MD -0.4, 95% CI -0.8 to -0.04, p=0.0296) (Appendix Table G82) (Le[79]). There was no longer any difference between groups as measured between 13 and 18 months (RD 0.1 episodes) and between 19 and 24 months (RD 0.1 episodes).

Cholesteatoma
No cholesteatomas were found in any patient through 24 months.

OME, Balance and coordination
These outcomes were not reported by the included study.

Functional and quality of life outcomes
The trial did not report any functional or quality of life outcomes, including attention and behavioral outcomes, academic achievement, speech and language development, auditory processing, patient quality of life, parent satisfaction with treatment/outcomes, patient satisfaction with treatment/outcomes, or pain

Healthcare utilization

Surgery

Tube (re)insertion was performed in a similar percentage of ears through 24 months between TT and control ears (5% vs. 7%, MD -2%, 95%CI -11% to 7%, p=NS) (Appendix Table G83) (Le[79]).

Medication usage, Number of office visits

These outcomes were not reported by any of the included studies.

4.2. Key Question 2: Harms

4.2.1. Number of studies retained

All studies included in key question 1 (30 RCTs (reported across 49 publications), 3 prospective cohort studies (reported across 7 publications), and 1 retrospective cohort study) were evaluated for harms. In addition, case series specifically designed to evaluate harms that had at least 500 patients and follow-up of 60% were included: of the 11 case series reviewed at full text level, 3 were included in the report; the remaining 8 publications were excluded after full text review (see Appendix C).

4.2.2. OME: Tubes versus watchful waiting (WW) or no surgery (by-child analysis)

Studies included

Five trials comparing TT to WW reported adverse events: TARGET[98,100] (mean age 5.2 years at enrollment) (CoE II), Paradise[70,114-118] (mean age 1.25 years at enrollment) (CoE I), Rovers[67,139-141] (mean age 1.6 years at enrollment) (CoE III), Mandel 1989[88] and Mandel 1992[89] (mean age not reported, age ranged from 0.6 to 12 years at enrollment) (CoE III). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus WW are reported in Appendix Table H1. Perforation was reported by three trials, but no comparative data were provided. TARGET[98,100] reported perforation in 1.3% of 635 ears that received tubes (including crossover patients). Mandel 1989[88] and Mandel 1992[89] reported that perforation occurred in 11.2% to 13.7% of all patients (including TT, WW, and myringotomy), but did not separate results out by treatment group. Paradise[70,114-118] reported perforation combined with another abnormality (tympanosclerosis, fibrosis, and/or segmental atrophy) occurred similarly between TT and WW groups (4.1% vs. 1.5%, p=NS). Tympanosclerosis was reported by two trials. Paradise[70,114-118] found no difference between TT and WW groups in the incidence of tympanosclerosis when evaluating patients as randomized (2.7% vs. 3.0%, p=NS) as well as when evaluating patients according to whether or not the received tubes (4.1% vs. 1.0%, p=NS), while TARGET[98,100] found that tympanosclerosis occurred in 20.2% of tubed ears and no unoperated ears (as-treated analysis) (p<0.001). Segmental atrophy was reported by one trial (Paradise[70,114-118]), which found that segmental atrophy was associated with the TT group (32.7% vs. 11.9% in the WW group, RD 20.7%, 95% CI 11.4% to 30.1%, p<0.01). This RCT reported that together, TT ears with tympanosclerosis and segmental atrophy had significantly higher hearing levels compared with TT ears with no abnormality (8.1 vs. 5.1 dB, p=0.02). Retraction pocket was only reported in combination with another abnormality (tympanosclerosis and/or atrophy) and occurred in 0.7% of patients in both TT and WW groups in one trial (Paradise[70,114-118]). Fibrosis was significantly less common in the TT group compared with the WW group in one trial (Paradise[70,114-118]) (0.7% vs. 7.5%, RD -6.8%, 95% CI -11.4% to 2.1%, p=0.004). Persistent otorrhea requiring hospitalization, intravenous antibiotics, and daily suctioning occurred similarly in the TT and WW groups in one trial (2.4% vs. 3.4%, p=NS) (Mandel 1989[88]); this adverse event occurred in 2.2% of all patients (including TT, WW, and myringotomy) in another trial (Mandel 1992[89]). Otorrhea that occurred three or more times within 12 months following treatment (i.e., chronic otorrhea) was reported by one trial (Rovers[67,139-141]) to be more significantly more common in the TT group compared with the WW group (25% vs. 5%, RD 19%, 95% CI 10% to 29%, p<0.01). Other adverse events were reported for the TT group only, including procedure-related infection (6.8% ears that received tubes) (TARGET[98,100]) and premature tube extrusion in 9% (Rovers[67,139-141]). Mandel 1989[88] reported no problems with anesthesia.

4.2.3. OME: Tubes (unilateral) versus no treatment (contralateral) (by-ear analysis)

Studies included

Four trials reported adverse events: Dempster[38] (mean age 5.7 years at enrollment) (CoE III), Lildholdt[83] (mean age 3.9 years at enrollment) (CoE III), Maw and Bawden[91-94] (mean age not reported, age range 2 to 9 years at enrollment) (CoE III), and Maw 1991[90] (mean age not reported, age range 3 to 9 years at enrollment) (CoE III). Results from two of these trials (Maw and Bawden[91-94], Maw 1991[90]) did not stratify harms data for patients who did versus did not undergo adenoidectomy; all results from these trials are presented here and not in other safety sections as to avoid duplicating conclusions. Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for unilateral TT versus no treatment in the contralateral ear are reported in Appendix Table H2. Perforation or attic retraction occurred similarly between groups at 6 and 12 months (RD ranged from -2.9% to 2.8%, p=NS) in one trial (Dempster[38]), and the incidence of attic retraction was not statistically different between groups at any time point through 120 months (RD ranged from -4.6% to -0.5%, p=NS) in one trial (Maw and Bawden[91-94]). Tympanosclerosis was significantly more common in the TT group (range, 20% to 48.6% of ears) than in the untreated group (range, 0% to 6.8%) as measured between 6 and 60 months in three trials, with risk differences ranging from 20.0% to 45.9% (Lildholdt[83], Dempster[38], Maw 1991[90]); one trial (Maw 1991[90]) further categorized tympanosclerosis as moderate to severe in 10.8% of TT ears at 6 months to 30.3% at 60 months (all cases in the untreated ear were mild). Similarly, atrophy occurred in 5.1% to 27.3% more ears randomized to TT (range, 5.6% to 34.8% of ears) versus ears randomized to no treatment (range, 0% to 7.6%) as measured between 12 to 120 months across two trials (Lildholdt[83], Maw and Bawden[91-94]). There was no difference in the incidence of atelectasis between groups at any time point between 12 and 120 months (RD ranged from -3.1% to 3.6%) in one trial. Further, there was no difference in the incidence of severe atelectasis between groups (2% vs. 1.5%); the 23 patients (in either group) with severe atelectasis had significantly more TT insertions than the 199 patients with no atelectasis (2.7 vs. 1.8, p=0.0095) ((Maw and Bawden[91-94]). The same trial found that minor scaring or thickening of the pars tensa was more 6.5% more common in the TT ear than the untreated ear at 12 months (14.0% vs. 7.5%, p=0.036), but there was no difference between groups for any other time point between 24 and 120 months. Other adverse events were reported for the TT group only, including perforation (0-0.75% ears) (Lildholdt[83]) and granulation tissue in the ear canal (4.5% ears) (Maw and Bawden[91-94]). No harms of general anesthesia were reported.

4.2.4. OME: Tubes versus Myringotomy

Studies included

Six RCTs reported adverse events. Of these, four trials randomized patients to either bilateral TT or myringotomy (D'Eredita 2006[35] (mean age 3.7 years at enrollment, CoE III), Gates 1987/1989[48,49] (mean age NR, age 4-8 years at enrollment, CoE II), Mandel 1989[88], Mandel 1992[89] (mean age NR, age 0.6-12 years at enrollment, CoE III), and two trials randomized children by ear to unilateral TT and contralateral myringotomy (Kent 1989[73] (mean age 5.3 years at enrollment, CoE III), Koopman 2004[76] (mean age 4.2 years at enrollment, CoE II)). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus myringotomy are reported in Appendix Table H3. Perforation occurred similarly between tubed and myringotomy patients (1.2% vs. 1.3%, p=NS, note that data include those who

underwent adenoidectomy) through 24 months in one trial (Gates[48,49]); Mandel 1989[88] and Mandel 1992[89] reported that perforation occurred in 11.2% to 13.7% of all patients (including TT, WW, and myringotomy), but did not separate results out by treatment group. Persistent otorrhea requiring hospitalization, intravenous antibiotics, and daily suctioning occurred similarly in the TT and myringotomy groups in one trial (2% vs. 0%, p=NS) (Mandel 1989[88]); this adverse event occurred in 2% of all patients (including TT, WW, and myringotomy) in another trial (Mandel 1992[89]). Koopman[76] reported one case of severe otalgia in the myringotomy ear two days post-surgery (0.4% myringotomy ears) as well as one patient with an epidermal pearl on the tympanic membrane that was removed by suction in an outpatient visit (0.4% myringotomy ears). Kent[73] reported no cases of post-operative nystagmus. Across all patients in the study (including those who underwent adenoidectomy) Gates[48,49] reported tube extrusion into the middle ear in 0.5% of patients; these patients required myringotomy and insertion of a new tube. The same trial also reported one case of necrosis of the long process of the incus in the TT group (0.8%) which required ossiculoplastic repair. Mandel 1989[88] reported no problems with anesthesia in either treatment group, D'Eredita[35] and Kent[73] reported no surgical complications, and Gates[48,49] reported no deaths.

4.2.5. OME: Tubes + Adenoidectomy vs. Myringotomy + Adenoidectomy

Studies included

Seven RCTs reported adverse events. Of these, four trials randomized patients to either bilateral TT or myringotomy and treated all patients with adenoidectomy [Casselbrant[24] (mean age 2.9 years at enrollment, CoE III), Gates 1987/1989[48,49] (mean age NR, age 4-8 years at enrollment, CoE II), Popova 2010[125] (mean age 5.1 years at enrollment, CoE III)] or adenotonsillectomy (Vlastos 2011[169] trial of sleep apnea patients with bilateral OME, mean age 4.5 years at enrollment, CoE III). Three trials randomized children by ear to unilateral TT and contralateral myringotomy and treated all patients with adenoidectomy: Ruckley 1988[142] (mean age 5.1 years at enrollment, CoE III), Shishegar 2007[152] (mean age NR, age 4-8 years at enrollment, CoE II), and To 1984[158] (mean age at enrollment, 7.5 years, CoE III). In addition, two prospective cohort studies published across five papers[16,74,81,160,161 #825] met the inclusion criteria and performed by-ear (rather than by-child) analysis, treating all patients with adenoidectomy (Tos 1983/1989, Bonding 1985, Khodaverdi 2013[16,74,160,161], mean age 3.9 years at enrollment, CoE III) or adenotonsillectomy (Leek 1979[81], mean age NR, age 2-15 years at enrollment, CoE II) and performing TT insertion in one ear and myringotomy in the opposite ear. One retrospective cohort study also reported harms (Caye-Thomasen 2008[26], mean age 3.9 years at enrollment, CoE III) and treated all patients with adenoidectomy (and tonsillectomy in some patients) and performed TT insertion in one ear and myringotomy in the contralateral ear. Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT+Ad versus myringotomy+Ad are reported in Appendix Table H4. Persistent perforation was relatively uncommon as reported in two trials, occurring in 1.2% to 3.2% of patients in the TT+Ad group compared with 0% to 1.3% of patients in the myringotomy+Ad group; these differences were not statistically meaningful (Casselbrant[24], Gates[48,49]); note that the Gates[48,49] trial also included those patients who did not undergo adenoidectomy in these results. One cohort study reported persistent perforation in 1% of tubed ears and 0% of myringotomy ears (p=NS) (Tos/Bonding/Khodaverdi[16,74,160,161]); another reported no perforations in tubed ears but did not report data for the myringotomy ears (Leek[81]). One trial reported no cases of permanent perforation in the myringotomy ears only (Ruckley[142]), and another reported subtotal perforation in 2% of tube ears but no data were reported for the myringotomy ear (To[158]). One retrospective cohort study reported no difference in perforation between TT and myringotomy ears at 36, 84, or 300 months (Caye-Thomasen[26]). Chronic otorrhea (≥3

episodes per year) occurred similarly between groups (2% vs. 0%, RD 2%, p=NS) through 12 months in one RCT (Popova[125]). One trial reported no cases of tympanosclerosis in either ear through 3 months (Ruckley[142]), another found that through a mean of 24 months follow-up, tympanosclerosis was more common in the tubed ears in one RCT (16% vs. 2%, RD 14.3%, 95% CI 4.1% to 24.5%, p=0.0083). One cohort study similarly found that tympanosclerosis was more common in tube ears as measured between 12 and 36 months (48% vs. 10% (intention to treat analysis), p<0.001; 48% vs. 19% (as-treated analysis), p<0.001) and between 82 and 84 months (59% vs. 13% (as-treated analysis), p<0.001) (Tos, Bonding, Khodaverdi[16,74,160,161]). The same cohort study reported that myringosclerosis occurred in significantly more tubed ears than myringotomy ears through 300 months (57% vs. 29%, p<0.001); the retrospective cohort study reported that over 300 months follow-up, myringosclerosis occurred in roughly 50% of the ears that underwent tube insertion compared with only 10% to 20% in those that received myringotomy only (p<0.0001 at all time points) (Caye-Thomasen[26]). The same retrospective cohort study found that atrophy was seen in 13% to 27% of ears following TT and in 8% to 12% of ears following myringotomy (p=0.009 at 25 years only). Pars tens atrophy occurred similarly between tubed and myringotomy ears between 12 and 36 months (9% vs. 10%) but was more common in tubed eats versus myringotomy ears when evaluated at 300 months (30% vs. 18%, p=0.0521). Retraction segments requiring tube reinsertion occurred similarly between ears in one trial (4% vs. 2%, p=NS) (To[158]). There was no difference between tube versus myringotomy ears in the incidence of attic retraction between 12 and 36 months (29.7% vs. 34.9%, p=NS), although stage II (i.e., moderate) attic retraction was less common in tubed ears (7.4% vs. 17%, p=0.0057) in one cohort study (Tos, Bonding, Khodaverdi[16,74,160,161]). The same study found that flaccida retraction was similar between ears when evaluated at 300 months (19% vs. 17% ears, p=NS), while the retrospective cohort study found no difference between ears at 36, 84, or 300 months in flaccida or tensa retraction (Caye-Thomasen[26]). Across all patients in the RCT (including those who underwent adenoidectomy) Gates[48,49] reported tube extrusion into the middle ear in 0.5% of patients; these patients required myringotomy and insertion of a new tube. Displacement of the tube occurred in 4.1% of tubed ears in one cohort study (Leek[81]), and premature extrusion was reported in 2.4 of TT+Ad patients in one trial (Popova[125]). Tube blockage occurred in 5.1% of TT+Ad patients in one trial (Popova[125]) and 5.5% of TT ears in another trial (Ruckley[142]); no data were reported for the control group. Tube occlusion was reported in 17% of TT ears in two trials (Ruckley[142], Shishegar[152]). There was no difference between groups in terms of difficulty during anesthesia in two trials (0-3.2% to 0%) (Casselbrant[24], Gates[48,49]). One RCT reported no tube-related complications (not specified) (Vlastos[169]) and another reported no deaths (Gates[48,49]).

4.2.6. OME: Tubes + Adenoidectomy vs. Adenoidectomy

Studies included

Three trials reported adverse events: Dempster[38] (mean age 5.7 years at enrollment, CoE III), Brown[19] (mean age not reported, range 4-10 years at enrollment, CoE III), and Maw and Bawden[91-94] (mean age not reported, range 2-9 years at enrollment). Data from of these trials (Maw and Bawden[91-94]) for all patients with or without adenoidectomy was reported in the section on tubes versus no treatment; the results are not duplicated here but are presented next to other data from this section in Appendix Table H5. All included studies randomized patients by ear; all patients underwent adenoidectomy. Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT+Ad versus Ad are reported in Appendix Table H5. Perforation was not present in any ears at the 60 month follow-up visit in one trial (Brown[19]); another trial reported similar incidence of

either perforation or retraction at both 6 months (5% vs. 3%, p=NS) and 12 months (11% in both ears) (Dempster[38]). Tympanosclerosis was significantly more common in TT ears than untreated ears at 6 months (40% vs. 0%, p<0.001) and 12 months (46% vs. 0%, p<0.001) in one trial (Dempster[38]) and at 60 months (42% vs. 0%, p<0.001) in another trial (Brown[19]). Attic retraction was present in 5% of TT ears and 0% of untreated ears at 60 months in one RCT (p=0.08) (Brown[19]); the same trial reported no difference in the incidence of retracted tympanic membrane at 60 months (18% vs. 16%, p=NS). One trial reported no immediate postoperative complications (Dempster[38]).

4.2.7. OME: Tubes vs. Myringotomy + Adenoidectomy

Studies included

Both RCTs reported adverse events; these trials randomized patients to either bilateral TT (no adenoidectomy) or bilateral myringotomy plus adenoidectomy: Casselbrant[24] (mean age 2.9 years at enrollment, CoE III), Gates[48,49] (mean age NR, age 4-8 years at enrollment, CoE II). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus myringotomy+Ad are reported in Appendix Table H6. No persistent perforations occurred in either group through 36 months in one trial (Casselbrant[24]); the other trial reported perforation in 1.2% of both TT groups (i.e., TT alone and TT+Ad) compared with 1.3% in both myringotomy groups (i.e., myringotomy alone and myringotomy+Ad) through 24 months (Gates[48,49]). In all patients in this trial (results not stratified by treatment group), the tube extruded into the middle ear in 0.5%, requiring myringotomy and tube reinsertion. The same trial reported necrosis of the long process of the incus in one patient in the TT group (0.8%); this required ossiculoplastic repair. Casselbrant[24] reported no difficulty during anesthesia in either group, and Gates[48,49] reported no deaths.

4.2.8. OME: Tubes vs. Adenoidectomy

Studies included

Although both trials that randomized patients and ears to either unilateral TT (no adenoidectomy) or unilateral no treatment plus adenoidectomy reported adverse events, data from of these trials (Maw and Bawden[91-94]) reported adverse events for all patients with or without adenoidectomy was reported in the section on tubes versus no treatment; the results are not duplicated here but are presented next to other data from this section in Appendix Table H5. Results from the other trial are reported here: Dempster[38] (mean age 5.7 years at enrollment, CoE III). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus Ad are reported in Appendix Table H7. Perforation or retraction occurred similarly in both ears through 6 months (6% vs. 3%, RD 3%, 95% CI -6% to 12%, p=NS) and 12 months (6% vs. 11%, RD -5%, 95% CI -18% to 9%, p=NS) in one trial (Dempster[38]). The same RCT reported that tympanosclerosis was associated with TT through 6 months (20% vs. 0%, p=0.0045) and 12 months (31% vs. 0%, p=0.0002). No immediate postoperative complications occurred.

4.2.9. OME: Tubes vs. Antibiotics

Studies included

One RCT (published across two papers) reported harms: Bernard[12] and Stenstrom[154] (mean age 4.9 years at enrollment, CoE III). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus Ad are reported in Appendix Table H8. Chronic perforation did not occur in any patients in either group through 18 months (Bernard and Stenstrom[12,154]). As evaluated between 72 and 120 months follow-up, the composite outcome of perforation, retraction, or atelectasis was 1.5 times more common in the TT group versus the antibiotics group (as randomized) (RR 1.5, 95% CI 1.2 to 1.9); when analyzed as treated, those who received tubes were 4.8 times as likely to have this outcome compared with those who never received tubes (RR 4.8, 2.2 to 10.6). Myringosclerosis occurred in 13% of TT patients through 18 months but no data were reported for the antibiotics group; when assessed between 72 and 120 months 66% of those who received tubes only once (25/38) had myringosclerosis compared with 15% (4/27) of those who never received tubes (p<00001). Through 18 months, other complications reported for the TT group only included superinfection (30%) and foreign body retraction (13%). Through this same time period, mild reactions to the sulfonamide were reported for the antibiotic group only, including: allergic reaction (6%), nausea (3%), and vomiting (0%). No serious side effects of the medication occurred.

4.2.10. AOM: Tubes vs. Antibiotics

Studies included

All four RCTs reported adverse events following tubes versus antibiotics for recurrent AOM: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III), El Sayed[43] (mean age 1.7 years at enrollment, CoE III), Gebhart[50] (mean age 1.7 years at enrollment, CoE III), and Gonzalez[54] (mean age 1.5 years at enrollment, CoE II). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus Ad are reported in Appendix Table H9. All tube-related harms were reported for those randomized to TT only, including perforation in 4% of patients (healed by 9 months) (Gebhart[50]) and in 13% of TT patients through 21 months (Casselbrant 1992[23]), persistent otorrhea in 0% (El Sayed[43]), premature extrusion requiring reinsertion in 7% of TT patients (El Sayed[43]), tube pushed into middle ear in 0% (Gebhart[50]), and adverse events related to general anesthesia in 0% (Gebhart[50]). One trial reported three or more episodes of otorrhea or AOM in 25% through 21 months; the study indicated that the majority of these events were otorrhea but did not provide specific data (or data for the antibiotics group) (Casselbrant 1992[23]). The same trial reported no suppurative complications in either group through 24 months. Persistent infection occurred in no TT patients (Gebhart[50]), and one trial reported that there were no adverse events related surgery, anesthesia, or medication in either group (Gonzalez[54]). Two trials reported adverse reactions to medication in 7% to 9% of patients the antibiotics group only (Casselbrant 1992[23], El Sayed[43]); these events included skin rash (Gebhart[50]) as well as suspected urticarial and vaginitis (Casselbrant 1992[23]).

4.2.11. AOM: Tubes vs. Placebo or No treatment

Studies included

All three RCTs reported adverse events following TT insertion versus placebo or no treatment for recurrent AOM: Casselbrant 1992[23] (mean age not reported, age range 0.6-2.9 years at enrollment, CoE III), Gonzalez[54] (mean age 1.5 years at enrollment, CoE II), and Kujala[77,78] (mean age 1.3 years at enrollment, CoE II). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus Ad are reported in Appendix Table H10; very little was reported in the way of harms. As reported in the previous section, Casselbrant 1992[23] reported perforation in 13% of TT patients and three or more episodes of otorrhea or AOM in 25% of TT patients but did not report data for the control group. There were suppurative complications in one trial (Casselbrant 1992[23]) and no serious adverse events in either group across two trials (Gonzalez[54], Kujala[77,78]).

4.2.12. AOM or OME: Tubes (unilateral) vs. Myringotomy or No treatment (contralateral)

Studies included

One RCT reported harms following TT insertion versus no treatment in the other ear in patients with AOM or OME: Le 1991[79] (mean age 2.3 years at enrollment, CoE III). Note that otorrhea and cholesteatoma were reported as efficacy/effectiveness outcomes are included in Key Question 1.

Harms

All harms for TT versus Ad are reported in Appendix Table H11. Permanent perforation occurred in 4% of TT ears and no control ears through 24 months. Tympanosclerosis was significantly more common in TT ears compared with myringotomy ears (57% vs. 19%, RD 38%, 95% CI 19% to 58%, p=0.001) and compared with untreated ears (57% vs. 7%, RD 50%, 95% CI 34% to 66%, p<0.01). While there was no difference in the incidence of retraction or atrophy through 24 months between TT and myringotomy ears (25% vs. 31%, RD -6%, 95% CI -27% to 15%, p=NS), retraction or atrophy was significantly more common in TT ears versus untreated ears (25% vs. 4%, RD 21%, 95% CI 8% to 34%, p=0.020) (Le[79]).

4.2.13. AOM or OME: Tubes

Studies included

Three case series were included that were designed to evaluate harms in more than 500 patients and had at least 80% follow-up: Golz 1999[53] (N=3714 patients with chronic OME (89%) or recurrent AOM (11%), Hoffman 2002[64] (N=3198 patients with either chronic OME or recurrent AOM (% of each not reported)), and Lindstrom 2004[84] (N=507 patients with chronic OME (62%) and/or recurrent AOM (45%) (10% had multiple diagnoses)).

Harms

All harms for TT reported in Appendix Table H12. Cholesteatoma occurred in 0.8% to 1.1% of TT patients across two case series (Golz[53], Lindstrom[84]), persistent perforation after tube extrusion in 1.3% of TT ears (Lindstrom[84]), and chronic otorrhea in 1.7% of TT ears ((Lindstrom[84]). The most common adverse event was a tube that remained in place for more than 2 years (12.1%), although only 11% (10/92) of these retained tubes were surgically removed. Major (anesthesia-related) perioperative complications were reported in one case series (Hoffman[64]) and included death (0%), laryngospasm (0.9%), desaturation (0.4%), bradycardia (0.1%), dysrhythmia (0.1%), and stridor (0.2%) (Hoffman[2]). Other

anesthesia-related perioperative complications reported by the same case series included upper airway obstruction (0.9%), post-operative patient agitation (5.7%), prolonged (>30 minutes) recovery (2.7%), and emesis (1.6%) (Hoffman[2]).

4.3. Key Question 3: Differential Efficacy and Harms in Subpopulations

4.3.1. Number of studies retained

For this key question, RCTs that stratified on patient characteristics of interest and formally evaluated statistical interaction (effect modification) were considered for inclusion. Subgroups of interest included otitis media duration, recurrent acute versus chronic otitis media, children at risk for developmental disabilities (i.e., permanent hearing loss (independent of otitis media) (including sensorineural hearing loss); speech and/or language delay or disorder; autism spectrum disorders; Down Syndrome; craniofacial disorders (e.g., cleft palate) that are associated with cognitive, speech, and/or language delays; blindness or uncorrectable visual impairment; developmental delay), age, sex, repeated exposure to large groups of children (e.g., daycare), race, or socioeconomic status. All 30 RCTs included to evaluate the efficacy or safety of TT versus comparators for OME or AOM were assessed.

4.3.2. OME: Tubes versus watchful waiting (WW) or no surgery (by-child analysis)

Studies included

One RCT formally evaluated effect modification: Rach[127,177] (mean age 3.3 years at enrollment) (CoE III). Two RCTs also stratified outcomes following TT versus WW into two or more patient subgroups: Paradise[70,114-118] (mean age 1.25 years at enrollment) (CoE I) and Rovers[67,139-141] (mean age 1.6 years at enrollment) (CoE III).

Differential efficacy

Rovers[67,139-141] found that baseline hearing levels significantly modified the effect of hearing improvement at 6 months such that patients with worse baseline hearing improved more following TT (versus WW) than those with better baseline hearing following (p=0.023 for the better ear, p=0.04 for the worse ear). No other exposures tested (history of adenoidectomy, season at randomization, number of upper respiratory tract infections since birth, hospital) modified this outcome; no data were reported. The One trial also found that no exposures tested (baseline hearing level, history of adenoidectomy, season at randomization, number of upper respiratory tract infections since birth, hospital) modified this outcome; no data were reported. All examined exposures were specified a priori, however it was not clear what (if any) hypotheses were made regarding effect modification of these subgroups at baseline.

Paradise[70,114-118] found no effect of any exposure tested on any of the outcomes evaluated at 3 years of age, although no formal test for interaction was performed. Exposures tested include baseline unilateral versus bilateral OME, baseline continuous versus discontinuous OME, and severity of hearing loss at baseline (using two different hearing level thresholds: 30 dB and 40 dB). Outcomes evaluated include expressive language (Peabody Picture Vocabulary Test, Number of Different Words, Mean Length of Utterance in Morphemes, Percentage of Consonants Correct), parent-child stress (Parenting Stress Index Short Form), and behavior (Child Behavior Checklist).

Rach[127,177] reported data that suggested that OME duration (3-6 months versus >6 months prior to treatment) had no impact on language development (Reynell test verbal expression and verbal

comprehension) at 6 months, although no formal tests for interaction were performed and group sizes were very small (range, 6-14 patients per treatment/subgroup).

Differential harms
None reported.

4.3.3. OME: Tubes (unilateral) versus No Treatment (contralateral)

Studies included
One RCT formally evaluated effect modification: Dempster[38] (mean age 5.7 years at enrollment) (CoE III). One other RCT also stratified outcomes following TT versus WW into two or more patient subgroups: Maw and Bawden[91-94] (mean age NR, age ranged from 2 to 9 years at enrollment) (CoE II).

Differential efficacy
Dempster[38] reported improvements in hearing levels at 6 and 12 months separately for boys (n=23) versus girls (n=12) by treatment group, although no formal test for interaction was performed. At six months, while boys and girls in the TT ear had similar improvements in hearing levels, boys in the untreated ear had less improvement than girls in the untreated ear. At 12 months, hearing improvement was similar across both genders and both treatment groups, suggesting no effect modification.

Differential harms
Maw and Bawden[91-94] evaluated the impact of OME duration on the development atelectasis and attic retraction (evaluated individually) during 120 months of follow-up. No formal test for interaction was done. It was unclear whether the duration of OME reflected that which had occurred before enrollment and/or after surgery, and the data includes patients who underwent adenoidectomy and/or tonsillectomy as well. The results suggested that in TT ears, there was not a significant difference in duration of OME in those who developed atelectasis or attic retraction versus those who did not, while in the untreated ears, patients who developed atelectasis or attic retraction had a significantly longer duration of OME than those who did not The authors also reported that atelectasis in both the TT and no treatment ears was not related to any of the baseline characteristics tested, although no formal test for interaction was done (age, earache history, duration of hearing loss, number of episodes of hearing loss, parental smoking).

4.3.4. OME: Tubes versus Myringotomy

Studies included
One RCT formally evaluated effect modification: Gates 1987/1989[48,49] (mean age NR, age 4-8 years at enrollment, CoE II). One other RCT also stratified outcomes following TT versus myringotomy into two or more patient subgroups: Mandel 1989[88] (mean age NR, age 0.6-12 years at enrollment, CoE III).

Differential efficacy
Gates[48,49] stated that a formal test for interaction was conducted to determine whether any prespecified baseline characteristics modified the outcomes of time with effusion as well as time to recurrence. No interaction was found between the group, outcomes, and any characteristic tested (age, sex, ethnic group, laterality of effusion, referral source), however no details or data were reported.

Mandel 1989[88] stratified patients at enrollment based on the presence or absence of "significant" baseline hearing loss (>20 dB bilaterally or >40 dB unilaterally on audiometry), although no formal test for interaction was performed. There was no clear impact of baseline hearing loss on any outcome reported (middle ear effusion, AOM, otorrhea, surgery, or speech recognition thresholds) following TT versus myringotomy. Group sizes were very small (range, 11-30 patients per treatment/subgroup).

Differential harms
None reported.

4.3.5. OME: Tubes + Adenoidectomy versus Myringotomy + Adenoidectomy

Studies included
One RCT formally tested for interaction: Gates 1987/1989[48,49] (mean age NR, age 4-8 years at enrollment, CoE II).

Differential efficacy
Gates[48,49] conducted a test for interaction to evaluate whether any prespecified baseline characteristics modified the outcomes of time with effusion as well as time to recurrence. No interaction was found between the group, outcomes, and any characteristic tested (age, sex, ethnic group, laterality of effusion, referral source), however no details or data were reported.

Differential harms
None reported.

4.3.6. OME: Tubes + Adenoidectomy versus Adenoidectomy

One RCT formally tested for interaction: Dempster[38] (mean age 5.7 years at enrollment) (CoE III).

Differential efficacy
Dempster[38] reported improvements in hearing levels at 6 and 12 months stratified by treatment and gender (boys (n=17) versus girls (n=20)), although no formal test for interaction was performed. At both 6 and 12 months, hearing improvement was similar across both genders and both treatment groups, suggesting no effect modification.

Differential harms
None reported.

4.3.7. OME: Tubes versus Myringotomy + Adenoidectomy

None reported.

4.3.8. OME: Tubes versus Adenoidectomy

None reported.

4.3.9. OME: Tubes versus Antibiotics

None reported.

4.3.10. AOM: Tubes versus Antibiotics

None reported.

4.3.11. AOM: Tubes versus Placebo or No Treatment

None reported.

4.3.12. AOM or OME: Tubes (unilateral) versus Myringotomy or No Treatment (contralateral)

None reported.

4.4. Key Question 4: Cost effectiveness

4.4.1. Number of studies retained

This review focused on economic studies that evaluated, synthesized and compared costs and treatment outcomes for at least two treatment alternatives. The primary focus was placed on studies that conducted full economic analyses using data from patients; studies that employed hypothetical cohorts only are summarized briefly. Of nine studies that were included for full-text review, one study (Hartman 2001[60]) met the full inclusion criteria, four studies met the inclusion criteria but used hypothetical cohorts only, and four studies were excluded (see Appendix C).

4.4.2. OME

Hartman 2001[60] conducted a cost-utility analysis by collecting costs alongside a RCT (Rovers[67,139-141]) of 187 Dutch children (mean age 19.4 months) with persistent bilateral OME treated with TT versus watchful waiting. All children had failed three successive hearing screening tests prior to inclusion in the study. Outcomes assessed were language development and time without effusion. Costs were calculated on the basis of actual costs rather than charges and converted to 1998 US dollars. The analysis was conducted from a societal perspective; both direct (i.e., medical) and indirect (e.g., travel expenses, non-prescription medication, home help) costs per patient were estimated using trial data, guidelines and diaries kept by the children's parents documenting all outpatient visits and any non-medical costs related to treatment. Diaries were corrected for missing periods by mean of the patient-year approach. ICERs were calculated. A regression analysis was performed to adjust for possible confounding factors and sensitivity analyses of study variables were conducted.

The results of the trial indicated that by 1 year there were no statistically significant differences in comprehensive or expressive language as measured by the Reynell test and the Schlichting test between the two groups, even though the mean duration of OME for those treated conservatively was 4.5 months longer than those treated with TT. In terms of cost, tube insertion was more expensive with a mean total cost per child of $454 versus $120 with watchful waiting ($p<0.001$). According to the sensitivity analysis, the incremental costs of TT insertion varied between $320 and $491 depending on the cost of the surgery (including day care and 3 visits to an ENT specialist) and the cost of an additional ENT visit. Non-medical costs were low in both groups. ICERs could not be calculated since no differences in language development were found; however, estimated ICERs were calculated using the bootstrapping technique which indicated higher costs for TT with no differences in effect. Based on

these results, the authors recommend that insertion of TT should not be a standard treatment in all children with persistent OME.

This is a reasonably well-conducted study (QHES score = 80/100). Its strengths are in its use of patient-level data from a RCT and regression and sensitivity analyses. However, according to the authors, there are a variety of factors that may limit its generalizability such as the children were selected from a population-based screening program (rather than based on symptoms), the potential for measurement error regarding OME duration, the relatively short time horizon used (1 year), and the fact that treatment with antibiotics for OME is rare in the Netherlands whereas it forms a substantial part of the total medical costs in the United States and other countries.

Economic evaluations that employed hypothetical cohorts only:
The National Institute for Health and Clinical Excellence (NICE) (2008)[107] commissioned a cost-utility analysis which evaluated TT, TT plus adenoidectomy, hearing aids, and "no active treatment" for the management of persistent bilateral OME (>3 months). Hearing loss was not explicitly stated as a baseline characteristic. The study evaluated the cost per QALY through 12 months (or longer using sensitivity analysis). A decision tree model was constructed using data from the published literature (including clinical studies, the 2006/2007 National Health Services (NHS) Tariff and other government documents, and guidelines) and the opinion of the Guideline Development Group, to compare these treatments in 10,000 hypothetical children younger than 12 years. The study made a number of assumptions including TT extrusion by 39 weeks, need for TT reinsertion and/or surgical removal in some patients, postoperative and other complications, and regular ENT, audiological, and general practitioner visits. The study assumed that hearing aid patients with OME at 21 months would continue with hearing aids but be offered TT insertion and that downstream costs would allow for mold replacement every 13 weeks, battery replacement every 4 weeks and hearing aid loss or breakage. The model assumed that children receiving "no active treatment" would have increased costs due to higher incidence of AOM episodes. QALY was calculated by assigning a utility value to the potential gain in hearing levels. A number of one-way sensitivity analyses were undertaken to assess to what extent uncertainty over certain parameter values was likely to be important in interpreting the baseline results. The authors concluded that TT was the optimal treatment strategy as it is associated with better hearing and lower costs; the ICER was £16,000 per QALY, which is below the £20,000 per QALY threshold used by NICE as a willingness-to-pay benchmark.

4.4.3. AOM

Economic evaluations that employed hypothetical cohorts only:
Berman 1994[11] conducted a theoretical cost-effectiveness analysis to evaluate different combinations of treatments (observation, antibiotics alone, corticosteroids alone, corticosteroids plus antibiotics, and tympanostomy tubes) for persistent AOM. The study evaluated the cost to clear the effusion within six months; it was assumed that patients and treatment would be re-evaluated at each of three visits. The analysis was performed from payer (i.e., private insurer or Colorado Medicaid) and family (e.g., travel costs, cost of parental time spent on obtaining medical care for the child) perspectives. A decision analysis was performed using a hypothetical clinical case involving an asymptomatic 13-month old boy with persistent (6-weeks duration) bilateral middle ear effusion despite initial antibiotic treatment; efficacy rates were determined from a meta-analysis of RCTs assessing the impact of corticosteroids and/or antibiotics. The study assumed that all children whose effusions persisted for three months despite medical treatment would receive TT insertion. The study concluded that the combination of treatments that was the most cost-effective in this hypothetical case of AOM was treatment with

corticosteroid plus antibiotics, a second antibiotic three weeks later if the patient was unresponsive to the first one, and referral for TT insertion another three weeks later if the patient still had persistent effusion. Costs to payers were the major cost-drivers, while cost of travel and lost wages were minimal.

Bisconni 1991[13] conducted a cost-utility analysis of TT compared with antibiotics plus continuous chemoprophylaxis for the treatment of AOM, defined as three or more episodes within 12 months by age six. Hearing loss was not explicitly stated as a baseline characteristic. The study evaluated the cost of curing the infection over an average of six follow-up visits. The analysis was performed from both payer and family perspectives; local charges were used to estimate costs (i.e., sum of professional fees and antibiotic costs). A decision-tree model was created using risk estimates for antibiotic failures, recurrence rates, and other pertinent values obtained from the published literature. The study assumed that either treatment strategy would inhibit the serious sequelae of otitis media (e.g., hearing loss, meningitis) and that patients who failed antibiotic therapy at 6 months would undergo TT insertion. The results indicated that antibiotics were associated with lower costs ($281 vs. $396) and a higher net benefit (utility 0.948 vs. 0.933) compared with TT. Sensitivity analyses indicated that adjustments for cost and baseline probabilities of initial cure and recurrence of AOM shifted the benefit to favor TT; change in utilities had no significant effect on the model behavior. The authors concluded that acute and prophylactic treatment with antibiotics is the preferred initial strategy, with TT insertion reserved for failure of antibiotic treatment.

4.4.4. OME or AOM

Economic evaluations that employed hypothetical cohorts only:

Gates 1996[47] conducted a cost-utility analysis of medical (i.e., antibiotics, chemoprophylaxis) and surgical (i.e., TT with and without adenoidectomy, adenoidectomy/myringotomy) treatment of AOM and chronic OME (>30 days duration) in a hypothetical cohort of children younger than 5 years of age. The study evaluated the cost per QALY. The analysis was performed from payer and family perspectives and was based on evidence from various sources (the published literature, published tables from federal surveys and health statistics, practice activity from a recent survey developed for this project, an analysis of the costs of OME publish by the Agency for Health Care Policy and Research in 1994, and costs from insurance claims). The study made a number of assumptions, including an average of 1.5 courses of antibiotics and 2.5 physician visits for a case of AOM, average length of effusion/resolution rates, subsequent treatment(s) for recurrences, TT extrusion by 24 months, impact of chronic effusion on hearing loss and developmental issues, and indirect costs (e.g., loss of work, travel expenses). The results indicated that cost per QALY for a single episode of AOM treated medically over 2 months would be $233 per 0.05 (total $4780); for recurrent AOM treated with TT over 24 months, $2173 per 0.16 ($6790 total); and for chronic OME treated with TT alone or in combination with adenoidectomy the cost per increase in utility would be $2141 per QALY and $2027 per QALY, respectively. Further, freedom from hearing loss and subsequent developmental disability as a result of surgical treatment would translate into a lifetime gain of 3.5 QALY for severely affected children. The authors conclude that overall medical therapy is more expensive than surgical treatment of OME and the latter is a cost-effective choice for children with severe and recurrent OME that fails to respond to conservative treatment.

5. Strength of Evidence (SoE) tables

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report. A summary of the critical outcomes for each key question are provided in the tables below and are sorted by comparator. Details of these and other outcomes are available in the report.

5.1. TT compared with Watchful Waiting (by-child analysis) for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus WW For OME	Quality	Age At Enrollment
Hearing Levels*	6-9 mos.	3 RCTs (COMET, TARGET, Rovers) N=522	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	At 6-9 months f/u, hearing levels were a mean of 4.39 dB lower (better) in the TT group (pooled MD: -4.39 dB, 95% CI -6.29 to -2.50 dB, p<0.00001). (All patients had bilateral OME and hearing loss at baseline.)	⊕⊕⊕◯ MODERATE	Age: 1.6-5.2 yrs. (range of means)
	12-18 mos.	3 RCTs (COMET, TARGET, Rovers) N=467	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	By 12-18 months f/u, hearing levels were similar between groups (pooled MD -0.45 dB, 95% CI -2.44 to 1.54 dB, p=0.66). (All patients had bilateral OME and hearing loss at baseline.)	⊕⊕⊕◯ MODERATE	Age: 1.6-5.2 yrs. (range of means)
	Age 6	1 RCT (Paradise) N=281	No serious risk of bias	Unknown consistency	No serious indirectness	No serious imprecision	No other considerations	At age 6, mean hearing levels were similar between TT and WW groups (MD for left ear: 0.70 dB, 95% CI -0.12 to 1.59; MD for right ear: 0.20 dB, 95% CI -0.93 to 1.33, p≥0.12 for both). (At baseline, 71.5% of patients had hearing levels that were 20dB or higher; mean baseline hearing levels were not reported.)	⊕⊕⊕⊕ HIGH	Mean age: 1.25 yrs. (range: 0.2-3 yrs.)
Speech And Language	6-9 mos.	3 RCTs (COMET, Rovers, Rach)	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	At 6 to 9 months, verbal comprehension (pooled SMD 0.09,	⊕⊕⊕◯ MODERATE	Age: 1.2-4.7 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus WW For OME	Quality	Age At Enrollment
Development: Reynell And/Or Schlichting Tests		N=393						95% CI -0.21 to 0.39, p=0.55) as measured by the Reynell test was similar between groups.		(range of means)
	6-9 mos.	3 RCTs (COMET, Rovers, Rach) N=393	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	No serious imprecision	No other considerations	Results at 6 to 9 months suggest no difference in expressive language between groups (pooled MD 0.03, 95% CI -0.42 to 0.49), p=0.90) as measured by the Reynell and/or Schlichting tests.	⊕⊕◯◯ LOW	Age: 1.2-4.7 yrs. (range of means)
	12-18 mos.	2 RCTs (COMET, Rovers) N=388	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	At 12 to 18 months, there was no difference between groups in verbal comprehension as measured by the Reynell test. One trial (Rovers) reported that the TT group had improved 0.7 month more than the WW group by 12 months (95% CI, -0.3 to 1.7, p=0.18); at 18 months the COMET trial reported a mean difference in standard scores that was 0.17 higher in the TT group (95% CI, -0.21 to 0.56, p=0.37).	⊕⊕⊕◯ MODERATE	Age: 1.2-2.9 yrs. (range of means)
	18 mos.	1 RCT (COMET) N=152	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 18 months, the adjusted mean difference in the Reynell test expressive language was 0.14 higher in the TT group (95% CI, -0.28 to 0.56, p=0.51).	⊕⊕⊕◯ MODERATE	Age: 1.2-2.9 yrs. (range of means)
Other Speech And Language Development Outcomes†	Age 3, 4, 6, 9-11 yrs.	1 RCT (Paradise) N=304-401	No serious risk of bias	Unknown consistency	No serious indirectness	No serious imprecision	No other considerations	At age 3, 4, 6, or 9 to 11 years, there were no differences between groups in various measures of language development†.	⊕⊕⊕⊕ HIGH	Mean age: 1.25 yrs. (range: 0.2-3 yrs.)
	Age 7-8 yrs.	1 RCT (COMET)	Serious risk of	Unknown consistency	No serious indirectness	Serious imprecision	No other considerations	At age 7 to 8 years, were no differences between groups in	⊕⊕◯◯ LOW	Mean age: 2.9 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus WW For OME	Quality	Age At Enrollment
		N=67	bias [1]			[3]		various measures of language development†.		(range: 1.2-4.7 yrs.)
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life (TAIQOL)	6 & 12 mos.	1 RCT (Rovers) N=165-176	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	No serious imprecision	No other considerations	There were no significant differences between groups at 6 or 12 months f/u in any subdomain of the TAIQOL, including vitality, appetite, communication, motoric, social, anxiety, aggression, eating, and sleeping domains.	⊕⊕⊕◯ MODERATE	Mean age: 1.6 yrs.
Cholesteatoma	≤36 mos. & At age 5	2 RCTs (Paradise, Mandel 1989) N=275	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	One small trial (N=59) reported no difference between TT and WW groups (0% vs. 3%) in cholesteatoma formation through 36 months in 0% (0/30) of TT patients and 3% (1/29) of WW patients, a difference which was not statistically significant. One trial reported no cases of cholesteatoma in any tubed ears (172 ears) when evaluated at age 5.	⊕⊕◯◯ LOW	Mean age: 1.25 yrs. in 1 RCT, NR by 1 RCT (range, 0.6-12 yrs.)
Perforation	≤24-36 mos.	3 RCTs (TARGET, Mandel 1989, Mandel 1992) N=169 plus 635 ears	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	Serious imprecision [4]	No other considerations	No comparative data were provided. One trial (TARGET) reported perforation in 1.3% of 635 ears that received tubes (including crossover patients). The two Mandel RCTs reported that perforation occurred in 11.2% to 13.7% of all patients (including TT, WW, and myringotomy), but did	⊕◯◯◯ INSUFFICIENT	Mean age: 5.2 yrs. in one trial, NR in 2 trials (range, 0.6-12 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus WW For OME	Quality	Age At Enrollment
								not separate results out by treatment group. No firm conclusions can be made.		
Chronic Otorrhea	≤12 mos.	1 RCT (Rovers) N=187	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	Otorrhea that occurred three or more times within 12 months following treatment (i.e., chronic otorrhea) was significantly more common in the TT group compared with the WW group (25% vs. 5%, RD 19%, 95% CI 10% to 29%, p<0.01).	⊕⊕◯◯ LOW	Mean age: 1.6 yrs.
	≤36 mos.	2 RCTs (Mandel 1989, Mandel 1992) N=89	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	Persistent otorrhea requiring hospitalization, intravenous antibiotics, and daily suctioning occurred similarly in the TT and WW groups in one trial (2.4% vs. 3.4%, p=NS) (Mandel 1989); this adverse event occurred in 2.2% of all patients (including TT, WW, and myringotomy) in another trial (Mandel 1992).	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-12 yrs.)
HTE-Improvement In Hearing*	6 mos.	1 RCT (Rovers) N=206	Serious risk of bias (-2) [1,6]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	One trial found that baseline hearing levels significantly modified the effect of hearing improvement at 6 months such that patients with worse baseline hearing improved more following TT (versus WW) than those with better baseline hearing following (p=0.023 for the better ear, p=0.04 for the worse ear). No other exposures tested (history of adenoidectomy, season at randomization, number of upper respiratory tract infections since	⊕◯◯◯ INSUFFICIENT	Mean age: 1.6 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus WW For OME	Quality	Age At Enrollment
								birth, hospital) modified this outcome; no data were reported. No firm conclusions can be made.		
HTE- Patient QoI	6, 12 mos.	1 RCT (Rovers) N=206	Serious risk of bias (-2)[1,6]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	One trial found that no exposures tested (baseline hearing level, history of adenoidectomy, season at randomization, number of upper respiratory tract infections since birth, hospital) modified quality of life as measured by the TAIQOL measure at 6 or 12 months; no data were reported. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 1.6 yrs.

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

†Speech and language outcome measures reported include:

- Wechsler Objective Language Dimensions including comprehension and oral expression at age 7-8 (COMET)
- Children's Nonword Repetitive Task at age 7-8 (COMET)
- Peabody Picture Vocabulary Test-revised at age 3, 4, & 6 (Paradise)
- Expressive Language including number of different words, mean length of utterance, and percentage of consonants correct-revised at age 3, 4, & 6 (Paradise)
- Phonological memory at age 4, & 6 (Paradise)
- Comprehensive Test of Phonological Processing: elision and rapid letter naming at age 9-11 (Paradise)

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effects across trials
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate for a dichotomous outcome: small sample size, rare outcome
6. Serious risk of bias in evaluation of HTE: the subgroup variables were specified at randomization, however the hypothesized direction was not stated; the subgroup hypothesis was not one of a smaller number tested

5.2. TT (unilateral) compared with No treatment (contralateral) (by-ear analysis only) for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT (Unilateral) Versus No Treatment (Contralateral) For OME	Quality	Age At Enrollment
Hearing Levels*	6 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Lildholdt) N=209 (418 ears)	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	No serious imprecision	No other considerations	At 6 months f/u, results from three studies (N=144) suggest a modest benefit (2-5 dB) with TT, while a fourth study (N=65) suggests a larger benefit (11 dB) with TT. Pooled data from 3 of these trials (N=137) suggest 6-month hearing levels were a mean of 6.5 dB lower (better) in the TT group (pooled MD -6.6, -14.8 to -7.8 dB, p=0.01) (3 RCTs, N=137). One of these trials (N=35) also found a slight benefit in air bone gap hearing levels at 6 months with TT versus no treatment (17.3 ± 11.3 vs. 22.6 ± 11.0, MD -5.3, 95% CI -10.6 to 0.02, p=0.0508). (All patients had bilateral OME and the majority had hearing loss at baseline.)	⊕⊕◯◯ LOW	Age: 3.9-6.0 yrs. (range of means in 3 RCTs); NR in 1 RCT (range, 2-9 yrs.)
	12 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Lildholdt) N=218-220 (438 ears)	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	Serious imprecision [3]	No other considerations	By 12 months f/u, overall hearing levels were similar between groups (pooled from 3 RCTs (N=150) MD -3.2 dB, -8.9 to 2.4 dB, p=0.26); MD from 1 RCT (n=70) of 0 dB). However, one of these trials (N=78) found significantly better hearing in the TT ear than the no treatment ear (MD -11.3 dB, -14.8 to -7.8); this trial had reinserted tubes in 34% of TT ears by 12 months. One trial (N=35) also	⊕◯◯◯ INSUFFICIENT	Age: 3.9-6.0 yrs. (range of means in 3 RCTs); NR in 1 RCT (range, 2-9 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT (Unilateral) Versus No Treatment (Contralateral) For OME	Quality	Age At Enrollment
								reported similar air bone gap hearing levels between groups at 12 months (17.9 vs. 17.2 dB). No firm conclusions can be made.		
	24 mos.	3 RCTs (Black, Maw & Bawden, Lildholdt) N=171-173 (344 ears)	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	Serious imprecision [3]	No other considerations	At 24 months f/u, overall hearing levels were similar between groups (pooled from 2 RCTs (N=102) MD -2.0 dB, -9.6 to 5.6 dB, p=0.30); MD from 1 RCT (n=70) of 0 dB). However, one of these trials (N=69) found significantly better hearing in the TT ear than the no treatment ear (MD -5.4 dB, -8.9 to -1.9); this trial had reinserted tubes in 64% of TT ears by 24 months. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Age: 3.9-6.0 yrs. (range of means in 2 RCTs); NR in 1 RCT (range, 2-9 yrs.)
	36 mos.	2 RCTs (Maw & Bawden, Lildholdt) N=105-113 (218 ears)	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	Serious imprecision [3]	No other considerations	At 36 months f/u, one trial (N=57-65) found significantly better hearing in the TT ear than the no treatment ear (MD -3.7 dB, -7.3 to -0.1); this trial had reinserted tubes in 66% of TT ears by 36 months. The other trial (N=48) found no difference between groups (MD of 0 dB). No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 3.9 yrs. (in 1 RCT); NR in 1 RCT (range, 2-9 yrs.)
	48 mos.	2 RCTs (Maw & Bawden, Lildholdt) N=81-89 (170 ears)	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 48 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: 3.9 yrs. (in 1 RCT); NR in 1 RCT (range, 2-9 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT (Unilateral) Versus No Treatment (Contralateral) For OME	Quality	Age At Enrollment
	60, 84, 120 mos.	1 RCT (Maw & Bawden) N=15-56 (35-103 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 60, 84, and 120 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: NR (range, 2-9 yrs.)
Speech And Language Development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Cholesteatoma		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Perforation	6-60 mos.	2 RCTs (Dempster, Lildholdt) N=169 (204 ears)	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision[4]	No other considerations	Perforation or attic retraction occurred similarly between groups at 6 and 12 months (RD ranged from -2.9% to 2.8%, p=NS) in one trial (N=35); another trial (134 ears) reported perforation in 0% to 0.75% of ears following tube extrusion.	⊕⊕◯◯ LOW	Age: 3.9-5.7 yrs. (range of means)
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
HTE-Improvement In Hearing*	6 & 12 mos.	1 RCT (Dempster) N=35 (70 ears)	Serious risk of bias (-2) [1,5]	Unknown consistency	No serious indirectness	Serious imprecision[4]	No other considerations	One trial reported improvements in hearing levels at 6 and 12 months separately for boys versus girls by treatment group, although no formal test for interaction was performed. At six months, while boys and girls in the TT ear had	⊕◯◯◯ INSUFFICIENT	Mean age: 5.7 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT (Unilateral) Versus No Treatment (Contralateral) For OME	Quality	Age At Enrollment
								similar improvements in hearing levels, boys in the untreated ear had less improvement than girls in the untreated ear. At 12 months, hearing improvement was similar across both genders and both treatment groups, suggesting no effect modification. No firm conclusions can be made.		

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Serious risk of bias in evaluation of HTE: the subgroup variable did not appear to be specified at randomization, nor was the hypothesized direction stated a priori; the subgroup hypothesis was one of a smaller number tested

5.3. TT compared with Myringotomy for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Myringotomy For OME	Quality	Age At Enrollment
Hearing Levels*	6 mos.	2 RCTs (Black, Kent) N=67	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 6 months f/u, hearing was better in the TT ear compared with the myringotomy ear: one RCT reported a mean improvement in hearing of 7.4 dB (95% CI, 1.4 to 13.4, p<0.05), and the other RCT reported that significantly fewer TT ears had "hearing impairment" (not defined) than those treated with thermal myringotomy alone (0% versus 17%, RD -17%, 95% CI -30% to -3%, p=0.0206).	⊕⊕◯◯ LOW	Age: 5.3-6.1 yrs. (range of means)
	12 mos.	2 RCTs (Black, D'Eredita) N=67	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 12 months f/u, hearing levels were similar in both groups: Black[14] reported mean hearing levels that were 3.7 dB better in the TT ear (95% CI -0.4 to 7.8), and D'Eredita 2006[35] reported that hearing levels were normal in both TT and myringotomy patient.	⊕⊕◯◯ LOW	Age: 3.7-6.1 yrs. (range of means)
	24 mos.	1 RCT (Black) N=277	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 24 months, hearing levels were similar in TT versus myringotomy ears (0.9 dB better in the TT ear, 95% CI -2.7 to 4.6).	⊕⊕◯◯ LOW	Mean age: 6.1 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Myringotomy For OME	Quality	Age At Enrollment
	0-24 mos.	1 RCT (Gates) N=277	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	From baseline through 24 months, TT patients had hearing loss (hearing levels ≥20 dB) at 7% to 8.5% fewer audiometry evaluations than myringotomy patients as measured in both the better ear (10.1 ± 14.1% vs. 18.6 ± 19.5% of visits, RD -8.5%, 95% CI -12.5% to -4.5%, p<0.001) and in the worse ear (30.4 ± 22.7% vs. 37.5 ± 25.3% of visits, RD -7.1%, 95% CI -12.8% to -1.4%, p=0.0145).	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
Speech And Language Development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Cholesteatoma	≤24-36 mos.	2 RCTs (Gates, Mandel 1992) N=353	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	There was no difference between groups for this relatively rare outcome. One trial (n=277) reported that no cholesteatomas formed through 24 months. The other trial (n=76) reported no cases of cholesteatoma in TT patients (0/37) and two cases in myringotomy patients (5% (2/39)) through 36 months, a difference	⊕⊕◯◯ LOW	Mean age: NR (range 0.6-12 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Myringotomy For OME	Quality	Age At Enrollment
								which was not statistically significant. One child was treated with tympanomastoid surgery and the other underwent TT insertion.		
Perforation	≤24-36 mos.	3 RCTs (Gates, Mandel 1989, Mandel 1992) N=660	Serious risk of bias [1]	Serious inconsistency [2]	No serious indirectness	Serious imprecision [4]	No other considerations	Persistent perforation occurred similarly between tubed and myringotomy patients (1.2% vs. 1.3%, p=NS) at 24 months in one trial (N=512, note data include adenoidectomy patients); two small trials (N=169 total) reported that perforation occurred in 11.2% to 13.7% of all patients (including TT, WW, and myringotomy), but did not separate results out by treatment group. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range, 0.6-12 yrs.)
Chronic Otorrhea	≤36 mos.	2 RCTs (Mandel 1989, Mandel 1992) N=89	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	Persistent otorrhea requiring hospitalization, intravenous antibiotics, and daily suctioning occurred similarly in the TT and myringotomy groups in one trial (2% vs. 0%, p=NS) (Mandel 1989); this adverse event occurred in 2% of all patients (including TT, WW, and myringotomy) in another trial (Mandel 1992). No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range, 0.6-12 yrs.)
HTE- Time With Effusion; Time To	≤24 mos.	1 RCT (Gates,) N=177	Serious risk of bias (-2) [1,6]	Unknown consistency	No serious indirectness	Unknown precision	No data reported	One trial conducted a test for interaction to evaluate whether any prespecified baseline	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range, 4-8 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Myringotomy For OME	Quality	Age At Enrollment
Recurrence								characteristics modified the outcomes of time with effusion as well as time to recurrence. No interaction was found between the group, outcomes, and any characteristic tested (age, sex, ethnic group, laterality of effusion, referral source), however no details or data were reported. No firm conclusions can be made.		

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate for a dichotomous outcome: small sample size, rare outcome
6. Serious risk of bias in evaluation of HTE: although the subgroups appear to be specified a priori, the hypothesized direction was not stated a priori; the subgroup was not one of a smaller number tested

5.4. TT + adenoidectomy versus Myringotomy + adenoidectomy for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
Hearing Levels*	3 mos.	1 RCT (To) N=108 (216 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Hearing levels at 3 months were significantly better in the TT ear than the myringotomy ear (17.1 vs. 21.4 dB, mean difference -4.3 dB (95% CI not reported or calculable), p<0.05) in one trial of adenoidectomy patients.	⊕⊕◯◯ LOW	Mean age: 7.5 yrs.
	3 mos.	1 RCT (Ruckley) N=36 (72 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Air bone gap hearing levels were similar between TT and myringotomy ears at 3 months (6.9 vs. 7.4 dB, mean difference -0.5 dB, 95% CI -2.4 to 1.4 dB, p=NS).	⊕⊕◯◯ LOW	Mean age: 5.1 yrs.
	6 mos.	2 RCTs (Popova, Vlastos) N=112	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 6 months, there was no difference in hearing levels between TT+Ad and myringotomy+Ad groups, with a mean difference between patients was 0.4 dB (95% CI -2.3 to 3.1 dB, p=NS) in one RCT (N=78) and -5.2 dB (i.e., lower in the TT group) (95% CI -12.2 to 1.8 dB, p=NS) in the other RCT of sleep apnea patients (N=34).	⊕⊕◯◯ LOW	Age: 4.5-5.1 yrs. (range of means)
	6 mos.	1 RCT (Black) N=37 (74 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 6 months f/u, there was no difference in mean hearing levels between TT and myringotomy ears in adenoidectomy patients (mean difference -2.8 dB, 95% CI -7.4 to 1.9 dB, p=NS).	⊕⊕◯◯ LOW	Mean age: 6.1 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
	6 mos.	1 RCT (Shishegar) N=30 (60 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Air bone gap hearing levels were similar between TT and myringotomy ears at 6 months (17.6 vs. 16.3 dB, mean difference 1.4 dB (95% CI not reported/calculable), p-value not reported).	⊕⊕◯◯ LOW	Mean age: NR (range, 4-8 yrs.)
	12 mos.	2 RCTs (Popova, Vlastos) N=109	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 12 months, mean hearing levels were similar between TT+Ad and myringotomy+Ad groups, with a mean difference between patients of 0.8 dB (95% CI -1.2 to 2.8 dB) in one RCT (N=78) and -2.3 dB (95% CI -9.9 to 5.3 dB) in the other RCT of sleep apnea patients (N=31).	⊕⊕◯◯ LOW	Age: 4.5-5.1 yrs. (range of means)
	12 mos.	2 RCTs (Black, To) N=91 (182 ears)	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 12 months, there was no difference in mean hearing levels between TT and myringotomy ears in adenoidectomy patients, with a mean difference between patients of -1.4 dB (95% CI not reported or calculable), p=NS) in one RCT (N=54) and 1.0 dB (95% CI -4.0 to 6.1 dB) in the other RCT (N=37).	⊕⊕◯◯ LOW	Age: 6.1-7.5 yrs. (range of means)
	12 mos.	1 RCT (To) N=108 (216 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	A similar proportion of TT and myringotomy ears in adenoidectomy patients had hearing levels that improved by more than 6 dB through 12 months (72% vs. 69% of ears, RD 4%, 95% CI -14% to 21%, p=NS)	⊕⊕◯◯ LOW	Mean age: 7.5 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
	≤24 mos.	1 RCT (Gates) N=155	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	There was no difference in the percentage of patients with hearing loss (hearing levels ≥20 dB) between groups through 24 months; results for TT+Ad and myringotomy+Ad were reported separately for the better ear (6.5% vs. 7.8% of patients had hearing loss, mean difference -1.3%, 95% CI -4.4% to 1.8%, p=NS) and the worse ear (22.4% vs. 22.0% of patients had hearing loss, mean difference 0.4%, 95% CI -5.3% to 6.1%, p=NS)	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
	24 mos.	1 RCT (Black) N=37 (74 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 24 months, there was no difference in mean hearing levels between TT and myringotomy ears in adenoidectomy patients, with a mean difference between patients of -0.7 dB, 95% CI -6.4 to 4.9 dB.	⊕⊕◯◯ LOW	Mean age: 6.1 yrs.
Speech And Language Development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life (OM-6, Range 1-7, Lower Scores=Better	6 mos.	1 RCT (Vlastos, sleep apnea patients) N=44	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 6 months, TT+Ad-Tons patients had significantly greater improvement (from baseline) in disease-specific quality of life scores (OM-6) compared with	⊕⊕◯◯ LOW	Mean age: 4.5 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
Quality Of Life)								myringotomy+Ad-Tons patients (-0.38 vs. 0.00, MD -0.38, 95% CI -0.64 to -0.12, p=0.0050).		
	12 mos.	1 RCT (Vlastos, sleep apnea patients) N=41	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 12 months, the difference from baseline was better in the TT+Ad group though the difference did not achieve statistical significance (-0.32 vs. 0.01, MD -0.33, 95% CI -0.75 to 0.09, p=0.1230). Mean scores at 12 months were also similar between groups (1.84 vs. 2.04, MD -0.20, 95% CI -0.57 to 0.17).	⊕⊕◯◯ LOW	Mean age: 4.5 yrs.
Cholesteatoma	≤24 mos.	1 RCT (Gates) N=301	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [5]	No other considerations	There were no cases of cholesteatoma in either group through 24 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
Perforation	≤24-36 mos.	3 RCTs (Casselbrant, Gates, Ruckley) N=591	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	Persistent perforation was relatively uncommon as reported in two trials, occurring in 1.2% to 3.2% of patients in the TT+Ad group compared with 0% to 1.3% of patients in the myringotomy+Ad group; these differences were not statistically meaningful (note that these data include patients who did not undergo Ad in one trial). One trial reported no cases of permanent perforation in 36 myringotomy	⊕⊕◯◯ LOW	Mean age: 2.9-5.1 in 2 RCT, NR by 1 RCT (range 4-8 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
								ears but no data were reported for the tubed ears.		
Chronic Otorrhea	≤12 mos.	1 RCT (Popova) N=78	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	Chronic otorrhea (≥3 episodes per year) occurred similarly between groups (2% vs. 0%, RD 2%, p=NS) through 12 months in one RCT.	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-12 yrs.)
HTE- Time With Effusion; Time To Recurrence	≤24 mos.	1 RCT (Gates) N=301	Serious risk of bias (-2) [1,6]	Unknown consistency	No serious indirectness	Unknown precision	No data reported	Gates conducted a test for interaction to evaluate whether any prespecified baseline characteristics modified the outcomes of time with effusion as well as time to recurrence. No interaction was found between the group, outcomes, and any characteristic tested (age, sex, ethnic group, laterality of effusion, referral source), however no details or data were reported. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: NR (range, 4-8 yrs.)

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate for a dichotomous outcome: small sample size and rare outcome
6. Serious risk of bias in evaluation of HTE: although the subgroups appear to be specified a priori, the hypothesized direction was not stated a priori; the subgroup was not one of a smaller number tested

5.5. TT + adenoidectomy versus Adenoidectomy (no surgery in ear) for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Ad For OME	Quality	Age At Enrollment
Hearing Levels*	6 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Brown) N=228 (457 ears)	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 6 months f/u, pooled results from three studies (N=173) (MD -3.72 dB (95% CI -5.8 to -1.7 dB, p=0.0004, I^2=0%) as well as a fourth RCT (N=55) (MD ~-2.3 dB) suggest a modest benefit with TT. One trial (N=37) also reported significantly better air bone gap hearing levels in the ears randomized to TT at 6 months (14.5 vs. 20.4 dB, MD -5.9 dB, 95% CI -10.5 to -1.3 dB, p=0.0136). (All patients had bilateral OME and the majority had hearing loss at baseline.)	⊕⊕◯◯ LOW	Age: 5.9-6.1 yrs. (range of means in 2 RCTs); NR in 2 RCTs (range, 2-10 yrs.)
	12 mos.	4 RCTs (Black, Dempster, Maw & Bawden, Brown) N=252 (505 ears)	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [3]	No other considerations	At 12 months f/u, pooled results from three studies (N=197) (MD -1.9 dB (95% CI -4.4 to 0.6 dB, p=0.14, I^2=0%) as well as a fourth RCT (N=55) (MD ~-1.0 dB) suggest no significant benefit with TT. One trial (N=37) also reported significantly better air bone gap hearing levels in the ears randomized to TT at 12 months (16.5 vs. 17.2 dB).	⊕⊕◯◯ LOW	Age: 5.9-6.1 yrs. (range of means in 2 RCTs); NR in 2 RCTs (range, 2-10 yrs.)

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Ad For OME	Quality	Age At Enrollment
	24 mos.	2 RCTs (Black, Maw & Bawden) N=137 (275 ears)	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 24 months f/u, pooled hearing levels from two RCTs (N=137) suggested no difference between ears (MD -1.9 dB, -4.4 to 0.56 dB, p=0.13, I^2=0%). No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Age: 3.9-6.0 yrs. (range of means in 2 RCTs); NR in 1 RCT (range, 2-9 yrs.)
	36, 48, 84, 120 mos.	1 RCT (Maw & Bawden) N=42-112 (85-222 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 36, 48, 84, and 120 months f/u, there was no difference between TT and no treatment ears in mean hearing levels.	⊕⊕◯◯ LOW	Mean age: NR (range, 2-9 yrs.)
	60 mos.	2 RCTs (Maw & Bawden, Brown) N=148 (297 ears)	Serious risk of bias [1]	Serious inconsistency[2]	No serious indirectness	Serious imprecision[3]	No other considerations	At 60 months f/u, one trial found no difference between TT and no treatment ears in mean hearing levels (-0.6 dB, 95% CI -2.9 to 1.7 dB); the other reported hearing levels that were 3 dB higher (worse) in the TT ear (MD 3 dB, p-value not reported). No firm conclusions can be made.	⊕⊕◯◯ INSUFFICIENT	Mean age: NR (range, 2-10 yrs.)
Speech And Language Development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT+Ad Versus Ad For OME	Quality	Age At Enrollment
Cholesteatoma	60 mos.	1 RCT (Brown) N=55 (110 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	One trial reported no cases of cholesteatoma at 60 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-10 yrs.)
Perforation	60 mos.	1 RCT (Brown) N=55 (70 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	There were no cases of perforation at 60 months in either ear.	⊕⊕◯◯ LOW	Mean age: NR (range, 4-10 yrs.)
Perforation Or Retraction	6 & 12 mos.	1 RCT (Dempster) N=37 (74 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	Perforation or retraction occurred similarly in both ears through 6 months (5% vs. 3%, RD 3%, 95% CI -6% to 12%, p=NS) and 12 months (11% in both ears) in one trial.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
HTE-Improvement In Hearing	6 & 12 mos.	1 RCT (Dempster) N=35 (70 ears)	Serious risk of bias (-2) [1,5]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	One trial reported improvements in hearing levels at 6 and 12 months stratified by treatment and gender, although no formal test for interaction was performed. At both 6 and 12 months, hearing improvement was similar across both genders and both treatment groups, suggesting no effect modification. No firm conclusions can be made.	⊕◯◯◯ INSUFFICIENT	Mean age: 5.9 yrs.

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Serious risk of bias in evaluation of HTE: the subgroup variable did not appear to be specified at randomization, nor was the hypothesized direction stated a priori; the subgroup hypothesis was one of a smaller number tested; in addition, the study violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)

5.6. TT versus Myringotomy + Adenoidectomy for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
Hearing Levels*	≤24 mos.	1 RCT (Gates) N=180	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [5]	No other considerations	Through 24 months, there was no difference between groups in the percentage of appointments with hearing levels ≥20 dB in the better ear (10.1% vs. 7.8% of appointments, MD 2.3%, 95% CI -9.2% to 5.5%, p=0.1606). However, TT+Ad patients had significantly more appointments with hearing levels *in the worse ear* that were 20 dB or higher (30.4% vs. 22.0% of appointments, MD 8.4%, 95% CI 2.9% to 13.9%, p=0.0028)	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
Speech And Language Development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality		0 studies						No evidence	⊕◯◯◯	

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Myringotomy+Ad For OME	Quality	Age At Enrollment
Of Life									INSUFFICIENT	
Cholesteatoma	≤24 mos.	1 RCT (Gates) N=301	Serious risk of bias[1]	Unknown consistency	No serious indirectness	Serious imprecision[5]	No other considerations	There were no instances of cholesteatoma in either group through 24 months.	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
Perforation	≤24 & 36 mos.	2 RCTs (Gates, Casselbrant) N=557	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[5]	No other considerations	Persistent perforation occurred similarly between tubed and myringotomy patients (0-1.2% vs. 0-1.3%) through 24 and 36 months in two trials (note data from one trial includes TT & TT+Ad versus myringotomy & myringotomy +Ad patients).	⊕⊕◯◯ LOW	Mean age: NR (range 4-8 yrs.)
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
HTE		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate for a dichotomous outcome: small sample size and rare outcome

5.7. TT versus Adenoidectomy for OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Ad For OME	Quality	Age At Enrollment
Hearing Levels*	6 mos.	2 RCTs (Dempster, Maw & Bawden) N=236	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 6 months, mean hearing levels were 3.45 dB better in the TT ear compared with the no treatment ear in adenoidectomy patients (pooled MD -3.45 dB, 95% CI -6.02 to -0.88 dB, p=0.008, I^2=0%) in 2 RCTs.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.; NR in 1 RCT (range, 2-9 yrs.)
	12 mos.	2 RCTs (Dempster, Maw & Bawden) N=236	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 12 months, there was no longer a statistical meaningful difference between groups in mean hearing levels (pooled MD -0.64 dB, 95% CI -2.86 to 1.58 dB, p=0.57, I^2=0%) in two RCTs.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.; NR in 1 RCT (range, 2-9 yrs.)
	24 mos.	1 RCT (Maw & Bawden) N=169	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 24 months f/u, hearing levels were similar between groups (20.9 vs. 20.0 dB, p=NS).	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
	36 & 48 mos.	1 RCT (Maw & Bawden) N=155-169	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	No other considerations	Hearing levels were 2.1 to 2.8 dB worse in the TT ear at 36 months f/u (19.8 vs. 17.0 dB, MD 2.8 dB, 95% CI 0.1 to 5.5 dB, p=0.0428) and 48 months f/u (18.7 vs. 16.6 dB, MD 2.1 dB, 95% CI 0.6 to 3.6 dB, p=0.0066) in one RCT.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
	84 & 120 mos.	1 RCT (Maw & Bawden) N=58-102	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision[3]	No other considerations	At 84 and 120 months f/u, there was no difference between TT and no treatment ears in mean hearing levels, with a mean difference between groups of 0.8 dB and 0.9 dB, respectively.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Ad For OME	Quality	Age At Enrollment
Speech And Language Development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Cholesteatoma		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Perforation Or Retraction	6 & 12 mos.	1 RCT (Dempster) N=72	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Perforation or retraction occurred similarly in both ears through 6 months (6% vs. 3%, RD 3%, 95% CI -6% to 12%, p=NS) and 12 months (6% vs. 11%, RD -5%, 95% CI -18% to 9%, p=NS) in one trial.	⊕⊕◯◯ LOW	Mean age: 5.9 yrs.
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Hte		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT.

5.8. TT versus Antibiotics for OME

Outcome	Follow-up	Studies N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of TT versus Antibiotics for OME	Quality	Age at enrollment
Hearing levels*	2 & 4 mos.	1 RCT (Bernard & Stenstrom) N=125	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Mean hearing levels were significantly better in the TT group versus the antibiotics group at 2 months (~11 vs. ~20 dB, p<0.001) and 4 months (~12 vs. ~17 dB, p=0.0132). At both time points, significantly fewer TT patients had hearing levels greater than 25 dB versus antibiotics patients (no data reported).	⊕⊕◯◯ LOW	Mean age: 4.7 yrs.
	6, 12, & 18 mos.	1 RCT (Bernard & Stenstrom) N=125	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	There was no difference in mean hearing levels at 6 months (~12 vs. ~13 dB, P=NS), 12 months (~14 vs. ~15 dB, N=NS), and 18 months (~11 in both groups). The percentage of patients with hearing levels over 25 dB was statistically similar between groups (no data reported).	⊕⊕◯◯ LOW	Mean age: 4.7 yrs.
	72-120 mos.	Subanalysis of 1 RCT (Bernard & Stenstrom) N=113	Serious risk of bias [1, 5] (-2)	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Between 72 and 120 months follow-up, there was no significant difference between groups as randomized in mean hearing levels (hearing was 2.1 to 4.7 dB higher in TT patients across different frequencies, p=0.15), however slightly more TT patients had hearing levels over 15 dB (RR 1.8, 95% CI 1.1 to	⊕⊕◯◯ INSUFFICIENT	Mean age: 4.7 yrs.

Outcome	Follow-up	Studies N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of TT versus Antibiotics for OME	Quality	Age at enrollment
								3.1). When analyzed as treated, the 86 patients who received tubes regardless of treatment allocation had significantly higher hearing levels across different frequencies than the 27 patients who never received tubes (5.1 to 10.8 dB higher, p<0.001), similarly, significantly more tubed patients had hearing levels higher than 15 dB (RR 3.8, 95% CI 1.3 to 11.3, p<0.005). No firm conclusions can be made.		
Speech and language development		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Parent satisfaction	72-120 mos.	Subanalysis of 1 RCT (Bernard & Stenstrom) N=65	Serious risk of bias [1,5] (-2)	Unknown consistency	No serious indirectness	Serious imprecision[4]	No other considerations	When measured between 72 and 120 months post-treatment, parent-reported treatment satisfaction was similar for children who received tubes only once (n=38) versus those who never received tubes (n=27) (92% vs. 81%, MD 11%, 95% CI -6% to 28%, p=NS). No firm conclusions can be made.	⊕⊕◯◯ INSUFFICIENT	Mean age: 4.7 yrs.
Patient quality of life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Cholesteatoma		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

Outcome	Follow-up	Studies N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of TT versus Antibiotics for OME	Quality	Age at enrollment
Perforation	≤18 mos.	1 RCT (Bernard & Stenstrom) N=60	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	There were no chronic perforations in the TT group (n=60) through 18 months. The composite outcome of perforation, retraction, or atelectasis was more common in the TT group than the antibiotics group as randomized (RR 1.5, 95% CI 1.2 to 1.9) or as treated (i.e., those who received tubes versus those who never received tubes) (RR 4.8, 95% CI 2.2 to 10.6).	⊕⊕◯◯ LOW	Mean age: 4.9 yrs.
Chronic otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
HTE		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Data reported for a subgroup of the patients in the original RCT; additional risk of bias arises because data were reported according to treatment rather than as randomized.

5.9. TT versus Antibiotics for AOM

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Antibiotics For AOM	Quality	Age At Enrollment
Hearing Levels*	≤24 mos.	1 RCT (Casselbrant 1992) N=163	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	Through 24 months, there was no difference between TT and antibiotics groups in the percentage of time spent with hearing levels above 15 dB (10% vs. 12% of time, 95% CI NR, p=NS).	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-2.9 yrs.)
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Cholesteatoma	≤24-30 mos.	2 RCTs (Casselbrant 1992, Gebhart) N=258	Serious risk of bias [1]	No serious inconsistency	No serious indirectness	Serious imprecision [5]	No other considerations	There were no cholesteatomas in either group through 24 months in one RCT (N=163) and through 30 months in the other RCT (N=95).	⊕⊕◯◯ LOW	Mean age: 1.7 yrs. NR by 1 RCT (range, 0.6-2.9 yrs.)
Perforation	≤21 mos.	2 RCTs (Casselbrant 1992, Gebhart) N=130	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	Perforation occurred in 3.7% TT patients (2/54) in one trial and healed by 9 months; another trial reported perforations in 13.2% of TT patients (10/76); of these 7 healed spontaneously within a few months and the remainder persisted for 5, 9, and 21 months but eventually healed spontaneously.	⊕⊕◯◯ LOW	Mean age: 1.7 yrs. NR by 1 RCT (range, 0.6-2.9 yrs.)
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Antibiotics For AOM	Quality	Age At Enrollment
HTE		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate: small sample size and rare outcome

5.10. TT versus Placebo or No Treatment for AOM

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Placebo Or No Treatment	Quality	Age At Enrollment
Hearing levels*	≤24 mos.	1 RCT (Casselbrant 1992) N=157	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	Through 24 months, TT patients spent 10% of the time with hearing levels above 15 dB in the better ear compared with 16% in the placebo group (95% CI NR, p-value NR).	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-2.9 yrs.)
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life	4 & 12 mos.	Subanalysis of 1 RCT (Kujala) N=81-85	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	There were no differences between treatment groups in ear-related quality of life as measured by a 10-point VAS scale as well as the disease-	⊕⊕◯◯ LOW	Mean age: 3.6 yrs.

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT Versus Placebo Or No Treatment	Quality	Age At Enrollment
								specific OM-6 at 4 and 12 months.		
Cholesteatoma	≤24 mos.	1 RCT (Casselbrant 1992) N=163	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision[5]	No other considerations	There were no cholesteatomas in either group through 24 months in one RCT.	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-2.9 yrs.)
Perforation	≤21 mos.	1 RCT (Casselbrant 1992) N=76	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [4]	No other considerations	Perforation occurred in 13.2% of TT patients (10/76); of these 7 healed spontaneously within a few months and the remainder persisted for 5, 9, and 21 months but eventually healed spontaneously.	⊕⊕◯◯ LOW	Mean age: NR (range, 0.6-2.9 yrs.)
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
HTE		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or wide confidence interval

5.11. TT (unilateral) versus Myringotomy or No Treatment for AOM or OME

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT (Unilateral) Versus Myringotomy Or No Treatment (Contralateral) For AOM Or OME	Quality	Age At Enrollment
Hearing Levels*	3, 6, & 9 mos.	1 RCT (Le 1992) N=37 (74 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Between 3 and 9 months follow-up, hearing levels were 3.4 to 3.7 dB better in the TT ear than the control ear: MD -3.4 dB at 3 months (95% CI -6 to -1 dB, p=0.02), MD -3.7 dB at 6 months (95% CI -7 to 0, p=0.05), MD -3.5 at 9 months (95% CI -6 to 0, p=0.02) in one RCT. Further, at 9 months, 32% of patients had hearing levels at least 5 dB lower in the TT ear (p=0.04).	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.
	12, 15, 18,m 24, >24 mos.	1 RCT (Le 1992) N=37 (74 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [3]	No other considerations	Between 12 and more than 24 months, hearing levels were statistically similar between groups, with mean differences ranging from -0.08 to 2.1 dB. At 17 and 24 months, 14% to 28% of patients had had hearing levels at least 5 dB lower in the TT ear, although the difference was not statistically significant.	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.
Parent Satisfaction		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
Patient Quality Of Life		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

Outcome	Follow-Up	Studies N	Risk Of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Impact Of TT (Unilateral) Versus Myringotomy Or No Treatment (Contralateral) For AOM Or OME	Quality	Age At Enrollment
Cholesteatoma	≤24 mos.	1 RCT (Le) N=57 (114 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [5]	No other considerations	There were no cholesteatomas in either group through 24 months in one RCT.	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.
Perforation	≤24 mos.	1 RCT (Le) N=57 (114 ears)	Serious risk of bias [1]	Unknown consistency	No serious indirectness	Serious imprecision [5]	No other considerations	Permanent perforation occurred in 4% of TT ears and no control ears through 24 months.	⊕⊕◯◯ LOW	Mean age: 2.3 yrs.
Chronic Otorrhea		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	
HTE		0 studies						No evidence	⊕◯◯◯ INSUFFICIENT	

f/u: follow-up; MD: mean difference; mos.: months; NC: not calculable; RD: risk difference; SMD: standardized mean difference; TT: tympanostomy tubes; WW: watchful waiting; yrs.: years

*Hearing levels measured by audiometry unless otherwise indicated.

1. Serious risk of bias: the majority of studies violated one or more of the criteria for good quality RCT related to the outcome reported (see Appendix for details)
2. Inconsistency: differing estimates of effect across trials: one suggests large effect while three cross the threshold of no clinically meaningful difference
3. Imprecise effect estimate for a continuous outcome: wide (or unknown) confidence interval and/or small sample size
4. Imprecise effect estimate for a dichotomous outcome: small sample size and/or confidence interval includes both negligible effect and appreciable benefit or harm with TT
5. Imprecise effect estimate: small sample size and rare outcome

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